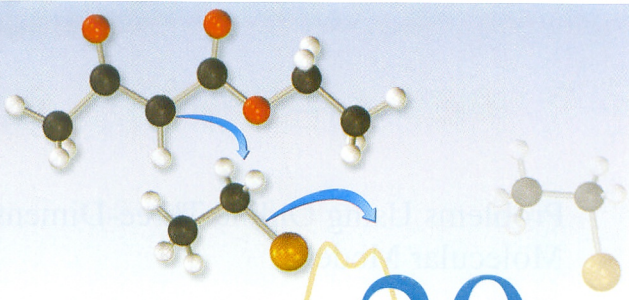
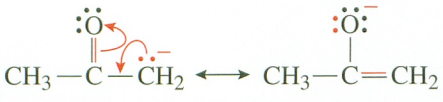


Enolate and Other Carbon Nucleophiles

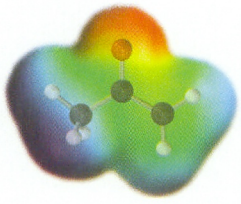
CHAPTER 20

REACTIONS THAT form carbon–carbon bonds are very important in organic chemistry because they enable larger, more complex organic molecules to be assembled from smaller, simpler ones. This process requires the reaction of a carbon nucleophile with a carbon electrophile. We have encountered a variety of carbon electrophiles, including alkyl halides in S_N1 and S_N2 reactions and the carbonyl carbon of aldehydes, ketones, and carboxylic acid derivatives in addition and substitution reactions. However, the carbon–carbon bond-forming reactions that we have seen have been limited because only a few carbon nucleophiles have been introduced so far. Cyanide and acetylide nucleophiles for the S_N2 reaction were presented in Chapter 10, and organometallic and ylide nucleophiles for reactions with compounds that contain the carbonyl group were discussed in Chapters 18 and 19.

Grignard reagents and related nucleophiles such as organolithium compounds are not very useful as nucleophiles in S_N2 reactions because they are too reactive. However, if there is a group bonded to the nucleophilic carbon that can help stabilize the pair of electrons, the resulting reagent can be very useful in reactions with alkyl halide electrophiles. One group that is particularly good at stabilizing a pair of electrons on an adjacent carbon is the carbonyl group. A carbanion adjacent to a carbonyl group is called an **enolate ion.** Enolate anions are perhaps the most important type of carbon nucleophile. These nucleophiles also give very useful reactions with carbonyl electrophiles.



Enolate anion derived from acetone



First, this chapter discusses the structure, stability, and methods for generation of enols and enolate anions. The reactions of these species as nucleophiles with halo-

MASTERING ORGANIC CHEMISTRY

- Predicting the Products of the Reactions of Enolate and Other Carbon Nucleophiles
- Understanding the Mechanisms of These Reactions
- Using These Reactions to Synthesize Compounds

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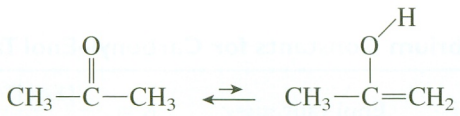
gens as electrophiles are discussed next. Then the use of enolate anions as nucleophiles in S_N2 reactions is presented. Their reactions with aldehyde, ketone, and carboxylic acid derivative electrophiles are discussed next. This is followed by the introduction of several other valuable carbon nucleophiles. A discussion of the use of these nucleophiles in conjugate additions precedes the final section, in which the use of these nucleophiles in synthesis is presented.

20.1 Enols and Enolate Anions

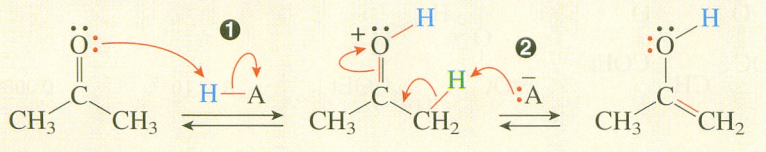
Section 11.6 discussed the acid-catalyzed addition of water to alkynes. The initial product of this reaction, called an enol, has a hydroxy group attached to one of the carbons of a CC double bond. The enol is unstable and rapidly converts to its tautomer, a carbonyl compound. The carbonyl and enol tautomers of acetone are shown in the following equation:



Carbonyl tautomer — Enol tautomer

The interconversion of the carbonyl and enol tautomers is catalyzed by either acid or base and occurs rapidly under most circumstances. The process requires only the addition of a proton to either the carbon or the oxygen atom and the removal of a proton from the other atom. In the acid conditions mechanism the proton is added first, while the base conditions mechanism involves removal of the proton in the first step. These mechanisms are shown in Figures 20.1 and 20.2.

Table 20.1 shows that the amount of enol tautomer that is present at equilibrium in the case of simple aldehydes and ketones is very small. Simple carboxylic acid derivatives, such as esters, have an even smaller enol content. However, 1,3-dicarbonyl compounds



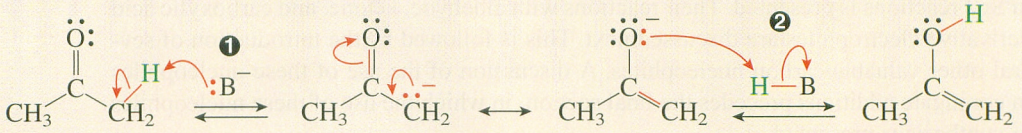
1 In acid a proton is first added to the oxygen of the carbonyl tautomer.

2 Then a proton is removed from the carbon.

For the reverse reaction the proton is first added to the carbon of the enol. Then one is removed from the oxygen.

Figure 20.1

MECHANISM OF INTERCONVERSION OF CARBONYL AND ENOL TAUTOMERS UNDER ACID CONDITIONS. This mechanism should be familiar to you. It was shown previously in Figure 11.6.



❶ In base a proton is first removed from the carbon of the carbonyl tautomer.

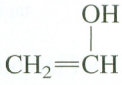
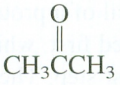
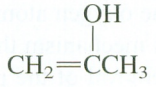
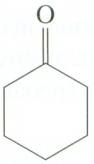
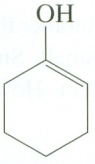
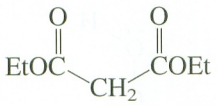
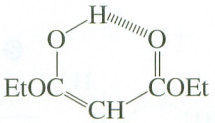
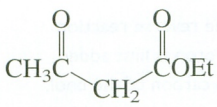
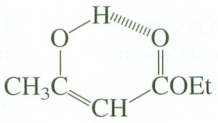
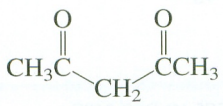
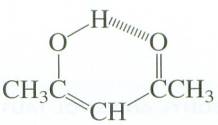
Resonance stabilization of the enolate anion makes it a weaker base than other carbanions, so it is easier to generate by acid–base reactions.

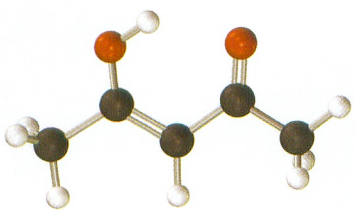
❷ Addition of a proton to the oxygen of the enolate anion produces the enol tautomer. If, instead, the proton is added to the carbon, the carbonyl tautomer forms in the reverse of the first step.

Figure 20.2

MECHANISM OF INTERCONVERSION OF CARBONYL AND ENOL TAUTOMERS UNDER BASE CONDITIONS.

Table 20.1 Equilibrium Constants for Carbonyl–Enol Tautomerization

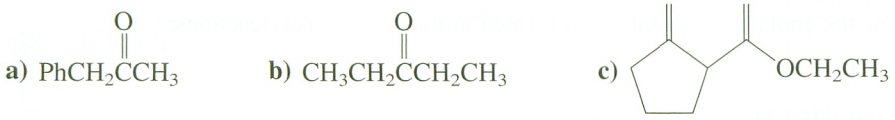
Carbonyl Tautomer	Enol Tautomer	$K = \frac{[\text{Enol}]}{[\text{Carbonyl}]}$	Enol Present
		6×10^{-7}	0.00006%
		5×10^{-9}	0.0000005%
		1×10^{-8}	0.000001%
		8×10^{-5}	0.008%
		9×10^{-2}	8%
		3	76%



(also called β-dicarbonyl compounds), such as the bottom three entries in Table 20.1, have a significantly larger amount of enol present at equilibrium. In these cases the enol is stabilized by conjugation of the CC double bond with the remaining carbonyl group and by intramolecular hydrogen bonding of the hydrogen of the hydroxy group with the carbonyl oxygen. The progressive increase in the enol content proceeding from the diester (0.008% enol) to the ketoester (8% enol) to the diketone (76% enol) again illustrates that enols involving ester carbonyl groups are less favorable than those involving ketone or aldehyde carbonyl groups.

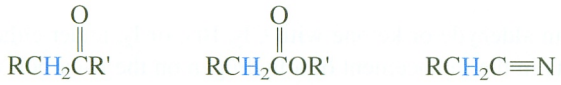
PROBLEM 20.1

Show all of the enol tautomers of these compounds. If more than one is possible, explain which is more stable.



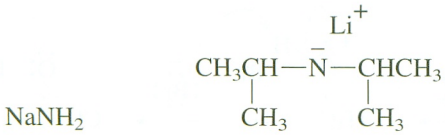
If a simple enol is generated by some reaction, such as the addition of water to an alkyne described in Section 11.6, the enol cannot be isolated because it rapidly converts to the more stable carbonyl tautomer. The lifetime of $CH_2{=}CHOH$, the simplest enol, is about 1 minute in aqueous solution at pH 7, about 1 second in acidic solution, and about 10^{-6} second in basic solution.

A hydrogen on a carbon adjacent to a carbonyl group (the α-carbon) is relatively acidic because the conjugate base is an enolate anion and is stabilized by resonance. A hydrogen on a carbon adjacent to a cyano group is relatively acidic for similar reasons. (It is important to remember that only hydrogens on the α-carbon are acidic because the carbanion is stabilized by resonance only when it is directly attached to the carbonyl or cyano group.) The pK_a's for the α-hydrogens of these compounds are in the range of 20 to 25.



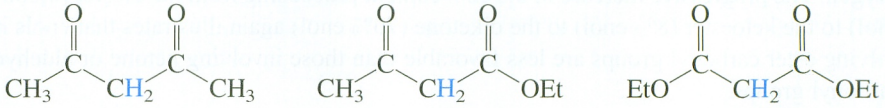
Ketone (or aldehyde)	Ester	Nitrile
$pK_a = 20$	$pK_a = 25$	$pK_a = 25$

Reaction of these compounds with a strong enough base removes a hydrogen to generate an enolate anion. The following bases, whose conjugate acids have pK_a's greater than 30, are all strong enough to completely deprotonate these compounds.



Sodium amide	Lithium diisopropylamide (LDA)	Sodium hydride
$pK_a = 38$	$pK_a = 38$	$pK_a = 35$

A hydrogen that is on a carbon adjacent to two carbonyl groups is even more acidic. The following β-dicarbonyl compounds are acidic enough that they can be completely deprotonated by bases such as ethoxide ion. (The pK_a of its conjugate acid, ethanol, is 16.)



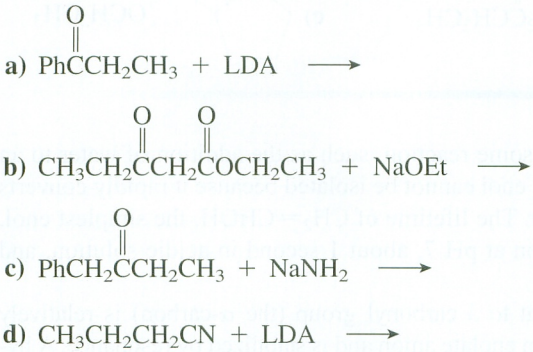
2,4-Pentanedione
$pK_a = 9$

Ethyl acetoacetate
$pK_a = 11$

Diethyl malonate
$pK_a = 13$

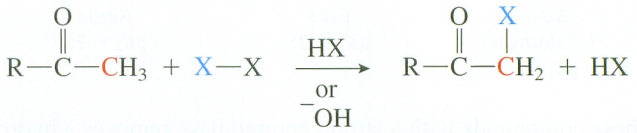
PROBLEM 20.2

Show the enolate or related anion formed in these acid–base reactions:

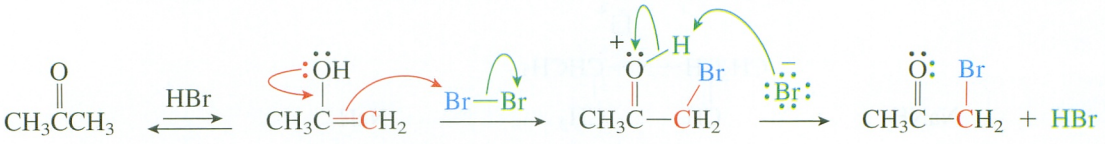


20.2 HALOGENATION OF THE α-CARBON

The reaction of an aldehyde or ketone with Cl_2, Br_2, or I_2, under either acidic or basic conditions, results in the replacement of a hydrogen on the α-carbon with a halogen.



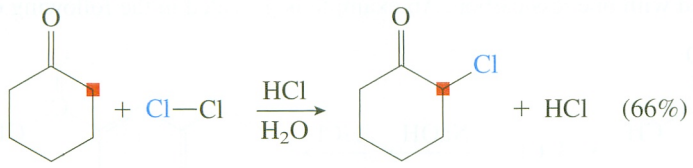
Under acidic conditions, the enol, generated according to the mechanism shown in Figure 20.1, acts as the nucleophile and attacks the electrophilic halogen.

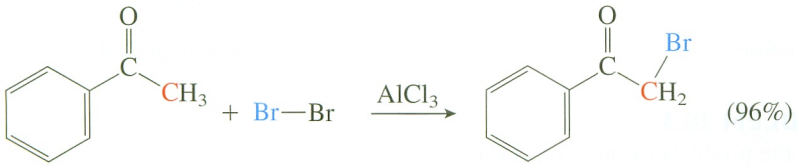


Enol

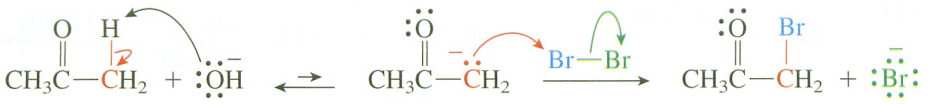
The presence of the halogen retards enolization, so it is possible to stop the reaction after the addition of a single halogen. This reaction can provide a useful way to add a halo-

gen to the α-carbon of a ketone, as long as the ketone is symmetrical or has only one reactive site. Some examples follow:





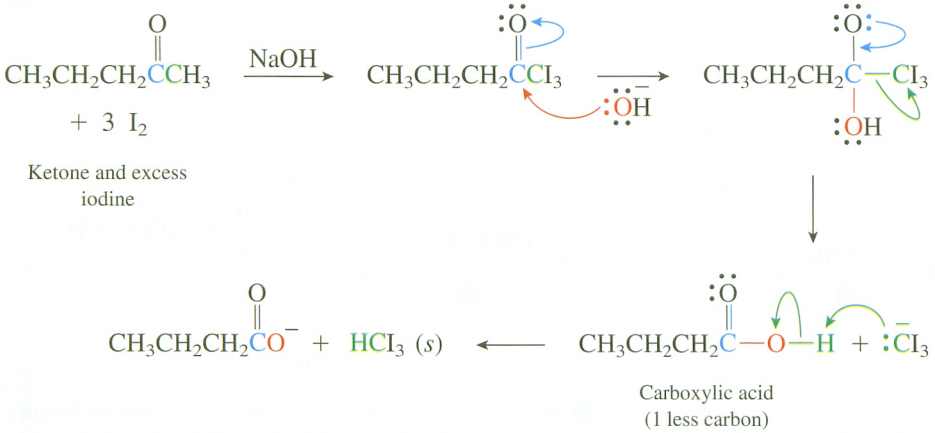
Under basic conditions, it is the enolate anion that acts as the nucleophile.



Enolate anion

In the **haloform reaction,** a ketone with a methyl group bonded to the carbonyl carbon is reacted with an excess of halogen in base. The methyl group is removed, and the ketone is converted to a carboxylic acid with one less carbon. This reaction first replaces a hydrogen on the methyl group with a halogen by the base mechanism just described. Because of the inductive electron-withdrawing effect of the halogen, the hydrogens on the α-carbon become more acidic after the first halogen is added, and a second halogen is added more rapidly than the first. This is followed by addition of a third halogen. Then hydroxide ion attacks the carbonyl carbon. The three halogens help the methyl carbon leave by stabilizing the resulting carbanion.

Haloform Reaction (Iodoform Reaction)

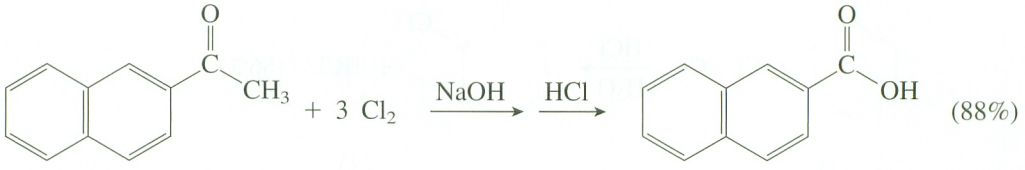


Ketone and excess iodine

Carboxylic acid (1 less carbon)

The cleavage reaction does not occur unless there are three halogens on the carbon, so only methyl groups are removed in this manner. The reaction with I_2 (iodoform reaction) has been used as a test for methyl ketones. The formation of iodoform (CHI_3),

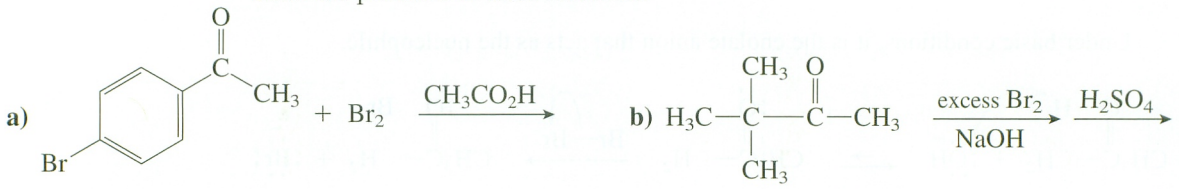
which precipitates as a yellow solid, provides a positive test for the presence of a methyl ketone. The reaction can also be used in synthesis to convert a methyl ketone to a carboxylic acid with one less carbon. An example is provided in the following equation:



A methyl ketone — A carboxylic acid

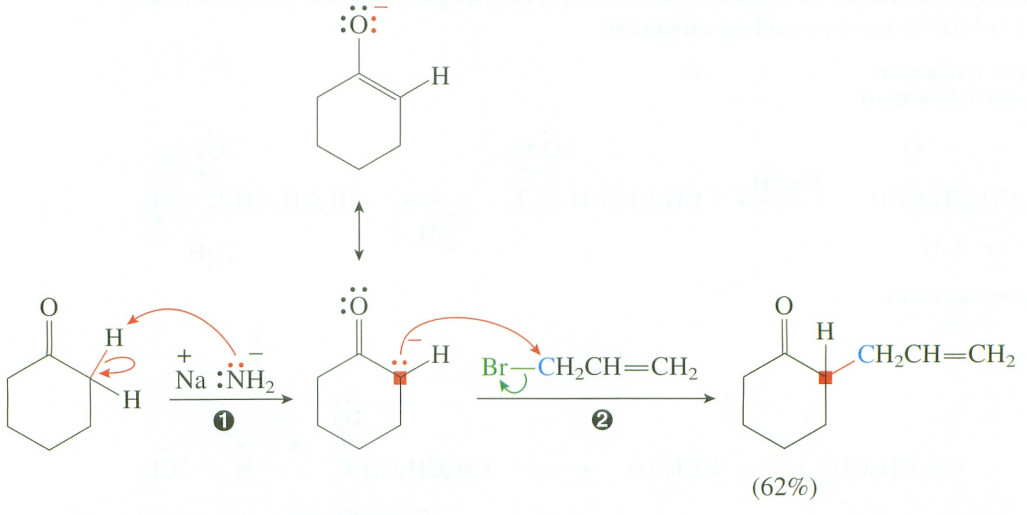
PROBLEM 20.3

Show the products of these reactions:



20.3 ALKYLATION OF ENOLATE ANIONS

Enolate anions generated from ketones, esters, and nitriles can be used as nucleophiles in S_N2 reactions. This results in the attachment of an alkyl group to the α-carbon in a process termed *alkylation*. Aldehydes are too reactive and cannot usually be alkylated in this manner. Alkylation of cyclohexanone is illustrated in the following equation:



❶ A strong base must be used to ensure complete deprotonation in this step. The solvent must not have any acidic hydrogens. An ether (diethyl ether, DME, THF, dioxane) or DMF is commonly used.

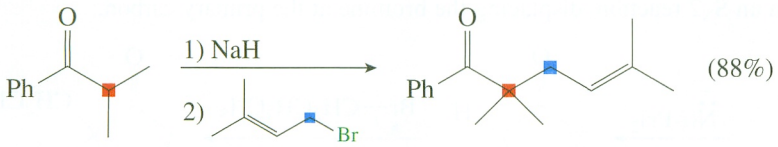
❷ Because this is an S_N2 reaction, it works only when the leaving group is attached to an unhindered carbon (primary or secondary). When the leaving group is attached to a tertiary carbon, E2 elimination occurs rather than substitution.

The base that is used must be strong enough to convert all of the starting ketone (or ester or nitrile) to the enolate anion. If it is not strong enough to do so, unwanted reactions of the enolate nucleophile with the electrophilic carbon of the remaining ketone may occur (see Sections 20.5 and 20.6). Lithium diisopropylamide (LDA) is often the base of choice. It is a very strong base but is not prone to give side reactions in which it acts as a nucleophile because of the steric hindrance provided by the bulky isopropyl groups. The alkyl halide (or tosylate or mesylate ester) is subject to the usual restrictions of the S_N2 mechanism. The leaving group may be bonded to a primary or secondary carbon but not to a tertiary carbon.

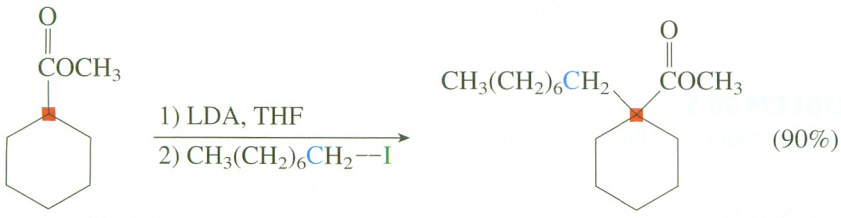
PROBLEM 20.4

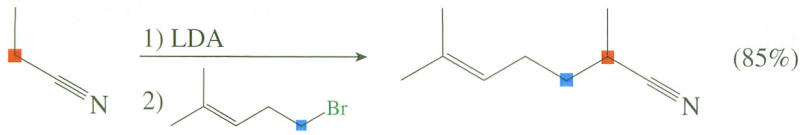
What reaction would occur if one attempted to use butyllithium to form the enolate anion of cyclohexanone?

To avoid the formation of two products, deprotonation of the ketone must produce a single enolate ion. Therefore, the ketone must be symmetrical, like cyclohexanone in the preceding example, or have a structure that favors the formation of the enolate ion at only one of the α-carbons, as is the case in the following example:

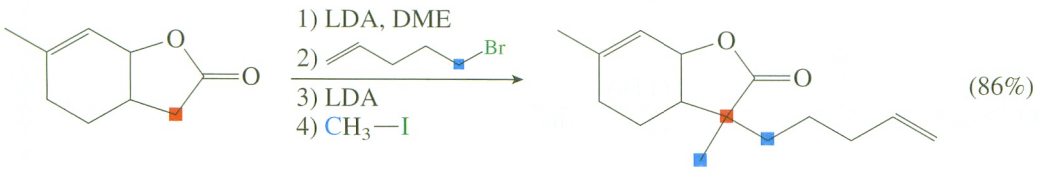


Esters and nitriles can also be alkylated by this procedure:



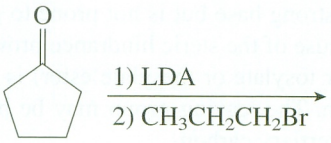


This last example shows how two alkyl groups can be added in sequence:



PRACTICE PROBLEM 20.1

Show the product of this reaction:

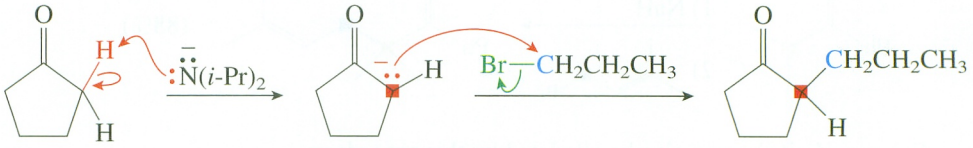


Strategy

The key to working problems of this type is the same as it has been in previous chapters. First identify the nucleophile and the electrophile. In these particular reactions the nucleophile is generated by removal of the most acidic hydrogen (one on the carbon α to the carbonyl or cyano group) to generate an enolate or related anion. This is the nucleophile in an S_N2 reaction.

Solution

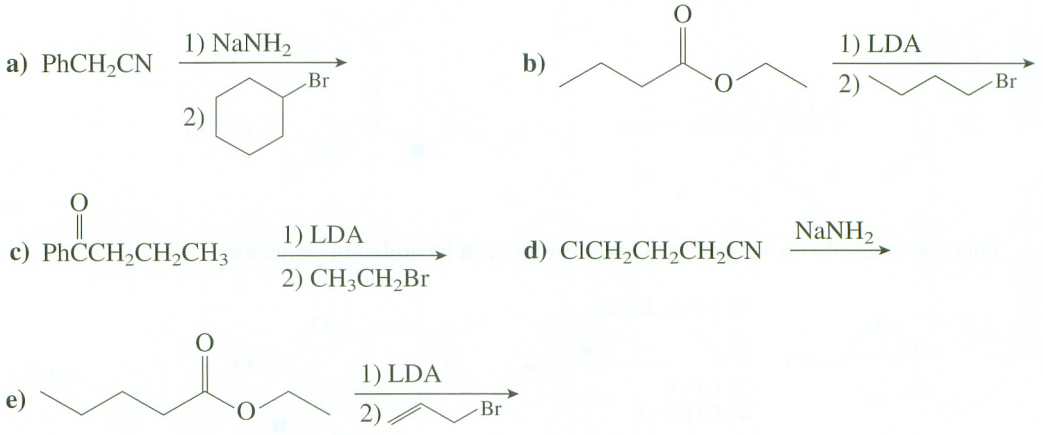
The diisopropylamide anion acts as a base and removes an acidic hydrogen from the carbon adjacent to the carbonyl group. The resulting enolate anion reacts as a nucleophile in an S_N2 reaction, displacing the bromine at the primary carbon.



Enolate ion nucleophile

PROBLEM 20.5

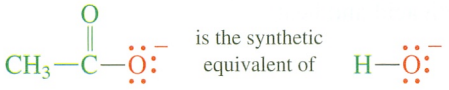
Show the products of these reactions:



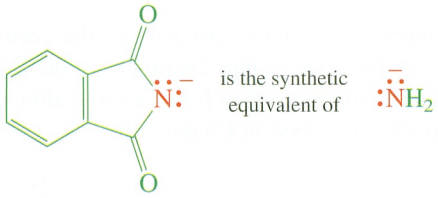
20.4 Alkylation of More Stabilized Anions

The nucleophiles described in the preceding section are strong bases and therefore are quite reactive. This high reactivity sometimes causes problems. We have seen before that one way to solve problems caused by a nucleophile that is too reactive is to attach a group to the nucleophilic site that decreases its reactivity. After this new, less reactive reagent, which causes fewer side reactions, is used in the substitution, the extra group is removed. Although it involves more steps, this overall process provides the same product, often in higher yield, as would be obtained by using the original nucleophile.

One example of this strategy is the preparation of alcohols using acetate anion as the synthetic equivalent of hydroxide ion in S_N2 reactions (see Section 10.2 and Figure 10.1).

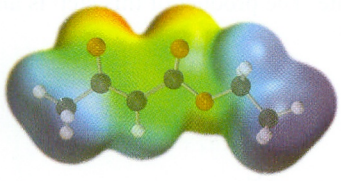


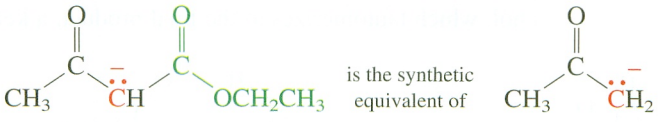
In a similar manner the conjugate base of phthalimide is used as the synthetic equivalent of amide ion for the preparation of primary amines in the Gabriel synthesis (see Section 10.6 and Figure 10.5).



In both of these cases a carbonyl group(s) is attached to the nucleophilic atom. Resonance delocalization of the electron pair makes the anion more stable. It is easier to generate, and its reactions are easier to control. After the substitution reaction has been accomplished, the carbonyl group(s) is removed, unmasking the desired substitution product.

Now suppose that we want to use the enolate anion derived from acetone ($pK_a = 20$) as a nucleophile in a substitution reaction. This anion requires the use of a very strong base to generate it, and its high reactivity often causes low yields of the desired product. Instead, we may choose to use its synthetic equivalent, the enolate anion derived from ethyl acetoacetate ($pK_a = 11$):



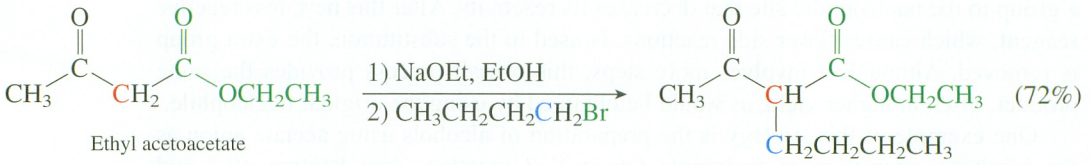


Enolate anion of ethyl acetoacetate

Enolate anion of acetone

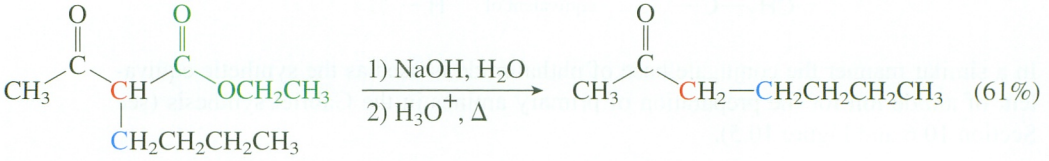
Alkylation of the enolate anion derived from ethyl acetoacetate followed by removal of the ester group is known as the **acetoacetic ester synthesis** and is an excellent method for the preparation of methyl ketones. The product of an acetoacetic ester synthesis is the same as the product that would be produced by the addition of the same

alkyl group to the α-carbon of acetone. First, the enolate ion is generated from the β-ketoester by the use of a moderate base such as sodium ethoxide. Then the enolate ion is alkylated by reaction with an alkyl halide (or alkyl sulfonate ester) in an S_N2 reaction. This step is subject to the usual S_N2 restriction that the leaving group be on a primary or secondary carbon.

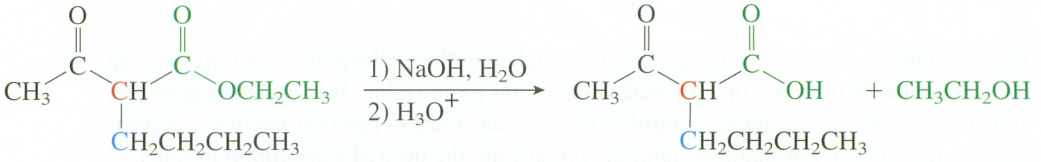


Ethyl acetoacetate

The ester group is removed by treating the alkylated β-ketoester with aqueous base, followed by treatment with acid and heat:

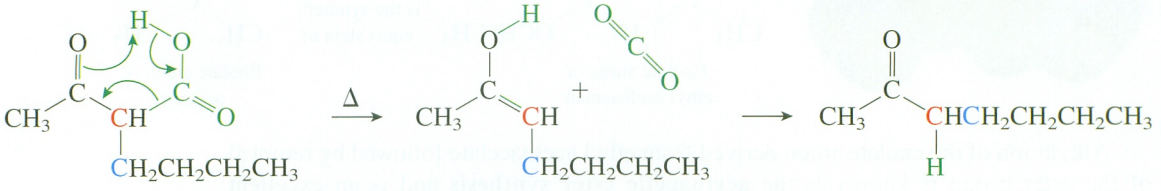


Let's examine the mechanism of the last part of the acetoacetic ester synthesis, which results in the loss of the ester group. Treatment of the β-ketoester with aqueous base results in saponification of the ester to form, after acidification, a β-ketoacid. The mechanism for this step was described in Chapter 19.



A β-ketoester A β-ketoacid

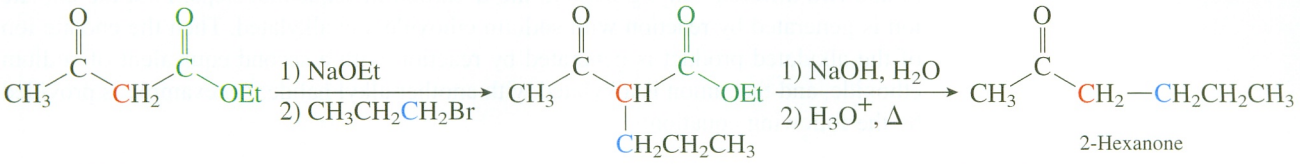
When the β-ketoacid is heated, carbon dioxide is lost. This step, a decarboxylation, occurs by a mechanism that is quite different from any other that we have encountered so far. Three bonds are broken and three bonds are formed in a concerted reaction that proceeds through a cyclic, six-membered transition state. The product of this step is an enol, which tautomerizes to the final product, a ketone:



An enol A methyl ketone

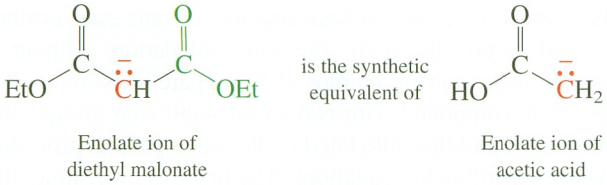
Note that simple carboxylic acids are quite stable and do not lose carbon dioxide when heated. For carbon dioxide to be eliminated, the acid must have a carbonyl group at the β-position so that the cyclic mechanism can occur.

Another example of the acetoacetic ester synthesis is shown in the following equation:

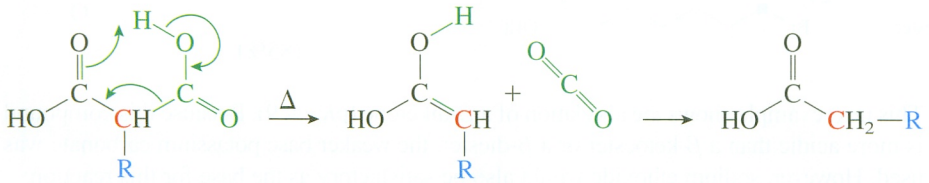


Note, again, that the final product, 2-hexanone, is the same product that would result from the reaction of the enolate anion of acetone with 1-bromopropane.

The **malonic ester synthesis** is similar to the acetoacetic ester synthesis. It begins with deprotonation of diethyl malonate ($pK_a = 11$) to produce an enolate anion that is the synthetic equivalent of the enolate anion derived from acetic acid:

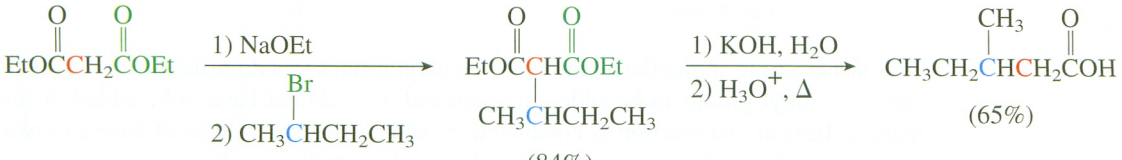


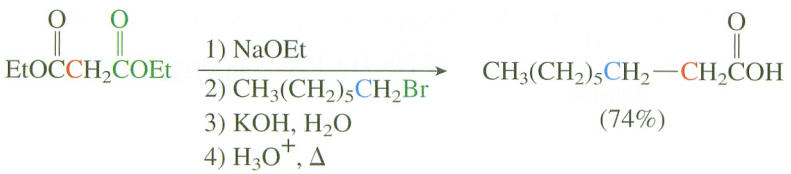
In the malonic ester synthesis this enolate ion is alkylated in the same manner as in the acetoacetic ester synthesis. Saponification of the alkylated diester produces a diacid. The carbonyl group of either of the acid groups is at the β-position relative to the other acid group. Therefore, when the diacid is heated, carbon dioxide is lost in the same manner as in the acetoacetic ester synthesis. The difference is that the product is a carboxylic acid in the malonic ester synthesis rather than the methyl ketone that is produced in the acetoacetic ester synthesis. The loss of carbon dioxide from a substituted malonic acid to produce a monoacid is illustrated in the following equation:



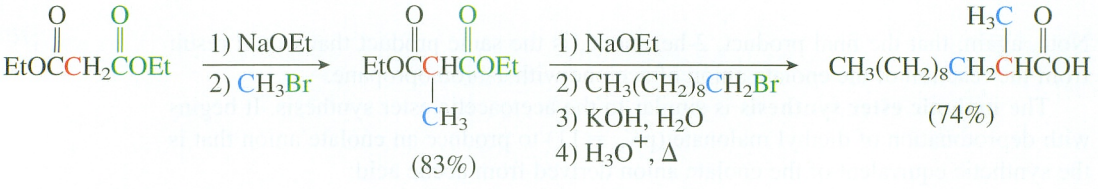
As was the case in the decarboxylation that occurs in the acetoacetic ester synthesis, it is the presence of a carbonyl group at the β-position of the carboxylic acid that allows carbon dioxide to be lost when the compound is heated.

Examples of the malonic ester synthesis are provided in the following equations:

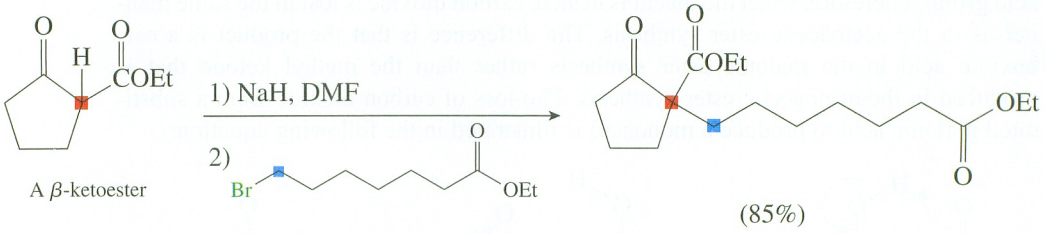




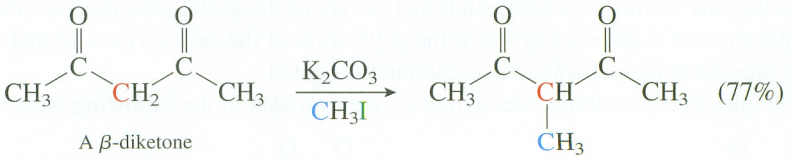
In both the acetoacetic ester synthesis and the malonic ester synthesis, it is possible to add two different alkyl groups to the α-carbon in sequential steps. First the enolate ion is generated by reaction with sodium ethoxide and alkylated. Then the enolate ion of the alkylated product is generated by reaction with a second equivalent of sodium ethoxide, and that anion is alkylated with another alkyl halide. An example is provided by the following equation:



Although the acetoacetic ester synthesis and the malonic ester synthesis are used to prepare ketones and carboxylic acids, the same alkylation, without the hydrolysis and decarboxylation steps, can be employed to prepare substituted β-ketoesters and β-diesters. In fact, any compound with two anion stabilizing groups on the same carbon can be deprotonated and then alkylated by the same general procedure. Several examples are shown in the following equations. The first example shows the alkylation of a β-ketoester. Close examination shows the similarity of the starting material to ethyl acetoacetate. Although sodium hydride is used as a base in this example, sodium ethoxide could also be employed.



This next example shows the alkylation of a β-diketone ($pK_a = 9$). Because this compound is more acidic than a β-ketoester or a β-diester, the weaker base potassium carbonate was used. However, sodium ethoxide would also be satisfactory as the base for this reaction:



This last example shows the addition of two alkyl groups to a dinitrile ($pK_a = 11$). Because the alkyl groups to be added are identical, they do not have to be added in sequence. Instead, the reaction is conducted by adding two equivalents of base and two equivalents of the alkylating agent, benzyl chloride, simultaneously:

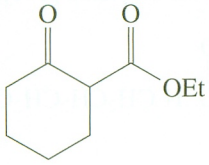
PROBLEM 20.6

Show the products of these reactions:

ORGANIC Chemistry Now™ Click *Coached Tutorial Problems* to practice **Alkylations of Enolate Anions.**

a) CH_3CCH_2COEt (O, O) → 1) NaOEt, EtOH; 2) $PhCH_2Br$ → 1) NaOH, H_2O; 2) H_3O^+, Δ

b) $EtOCCH_2COEt$ (O, O) → 1) NaOEt, EtOH; 2) $CH_3CH_2CH_2Br$ → 1) NaOH, H_2O; 2) H_3O^+, Δ

c)  → 1) NaOEt, EtOH; 2) CH_3CH_2Br

d) CH_3CCH_2COEt (O, O) → 1) NaOEt, EtOH; 2) $CH_3CH_2CH_2CH_2Br$; 3) NaOEt, EtOH; 4) CH_3I → 1) NaOH, H_2O; 2) H_3O^+, Δ

e) $N{\equiv}CCH_2CCH_3$ (O) → 1) NaOEt, EtOH; 2) $CH_3CH_2CH_2Cl$

PRACTICE PROBLEM 20.2

Show a synthesis of 2-heptanone using the acetoacetic or malonic ester synthesis:

$CH_3CH_2CH_2CH_2CH_2CCH_3$ (O)

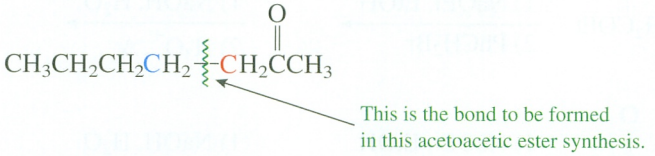
2-Heptanone

Strategy

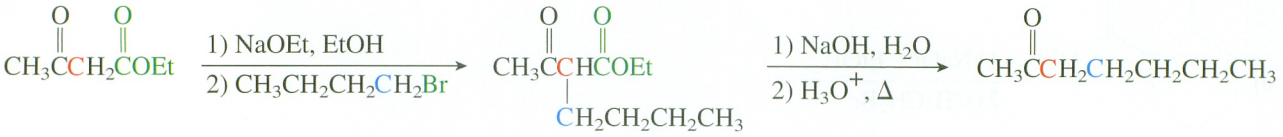
Decide which synthesis to use. The acetoacetic ester synthesis is used to prepare methyl ketones, and the malonic ester synthesis is used to prepare carboxylic acids. Both syntheses provide a method to add alkyl groups to the α-carbon. Therefore, next identify the group or groups that must be added to the α-carbon. Remember that the α-carbon is the nucleophile, so the groups to be attached must be the electrophile in the S_N2 reaction; they must have a leaving group bonded to the carbon to which the new bond is to be formed.

Solution

The acetoacetic ester synthesis is used to prepare methyl ketones such as this. In this example, a butyl group must be attached to the enolate nucleophile.

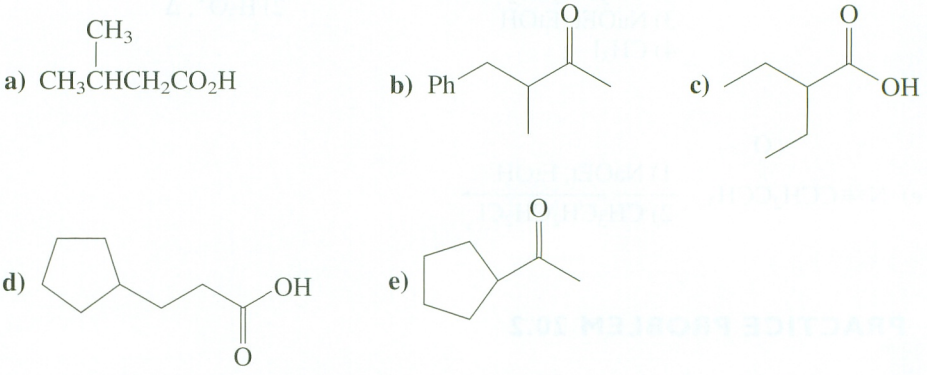


Use a base to generate the enolate anion nucleophile. Then add the alkyl group with a leaving group on the electrophilic carbon. Finally, decarboxylate the alkylated product.



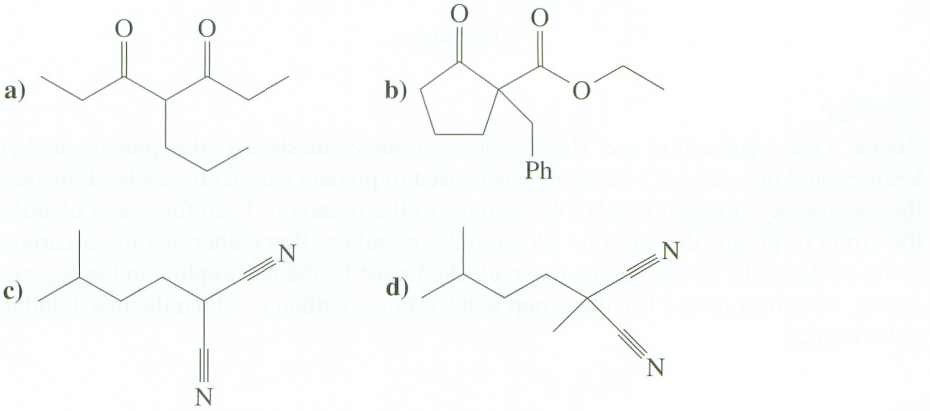
PROBLEM 20.7

Show syntheses of these compounds using the acetoacetic or malonic ester syntheses:



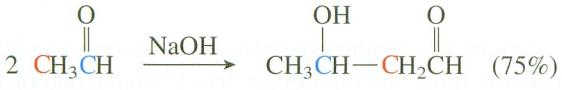
PROBLEM 20.8

Show how these compounds could be synthesized using alkylation reactions:



20.5 THE ALDOL CONDENSATION

You may have noticed that aldehydes were conspicuously absent from the examples of alkylation reactions presented in Sections 20.3 and 20.4. This is due to the high reactivity of the carbonyl carbon of an aldehyde as an electrophile. When an enolate anion nucleophile is generated from an aldehyde, under most circumstances it rapidly reacts with the electrophilic carbonyl carbon of an un-ionized aldehyde molecule. Although this reaction, known as the **aldol condensation,** interferes with the alkylation of aldehydes, it is a very useful synthetic reaction in its own right. The aldol condensation of ethanal is shown in the following equation:



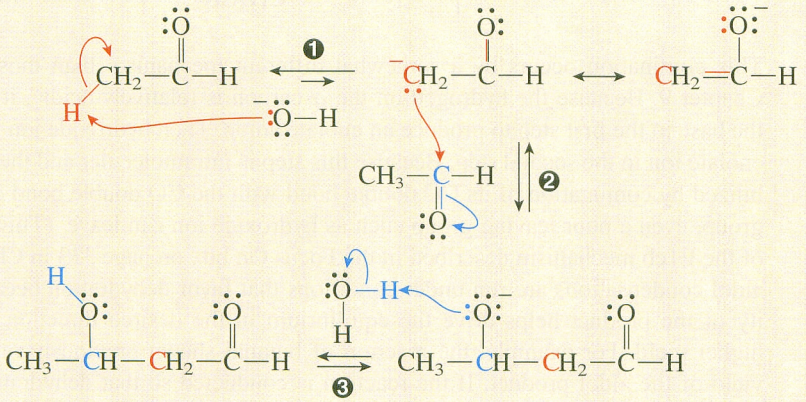
Ethanal — Aldol (3-hydroxybutanal)

The product, 3-hydroxybutanal, is also known as aldol and gives rise to the name for the whole class of reactions.

The mechanism for this reaction is shown in Figure 20.3. For this mechanism to occur, both the enolate anion derived from the aldehyde and the un-ionized aldehyde must be present. To ensure that this is the case, hydroxide ion is most commonly used as the base. Because hydroxide ion is a weaker base than the aldehyde enolate anion, only a small amount of the enolate anion is produced. Most of the aldehyde remains

❶ The base, hydroxide ion, removes an acidic hydrogen from the α-carbon of the aldehyde. The conjugate base of the aldehyde is a stronger base than hydroxide, so the equilibrium for this first step favors the reactants.

However, enough enolate ion nucleophile is present to react with the electrophilic carbonyl carbon of a second aldehyde molecule.



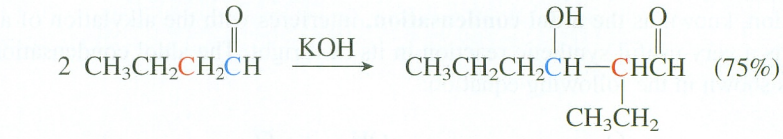
This part of the mechanism is just like the mechanism for the addition reactions of Chapter 18. ❷ The enolate nucleophile adds to the carbonyl carbon of a second aldehyde molecule, and ❸ the negative oxygen removes a proton from water. This step regenerates hydroxide ion, so the reaction is base catalyzed.

Figure 20.3

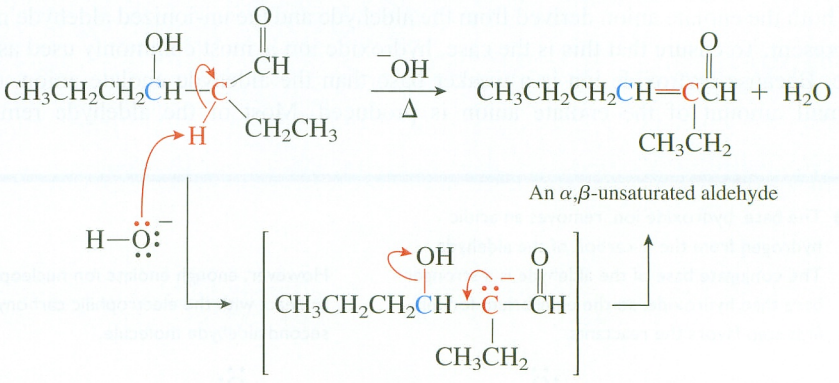
MECHANISM OF THE ALDOL CONDENSATION.

ORGANIC Chemistry Now™ Click *Mechanisms in Motion* to view the **Mechanism of the Aldol Condensation.**

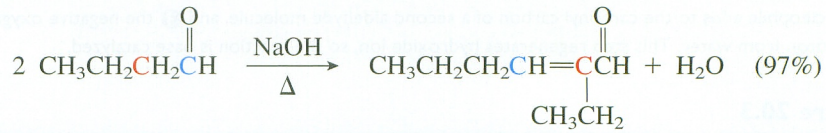
un-ionized and is available for reaction as the electrophile. Note that the strong bases described in Section 20.3, which would tend to convert most of the aldehyde molecules to enolate ions, are not used in aldol condensations. The addition of the enolate nucleophile to the aldehyde follows the same mechanism as the addition of other nucleophiles that were described in Chapter 18. Remember that the α-carbon of one aldehyde molecule bonds to the carbonyl carbon of a second aldehyde molecule, as illustrated in the following example:



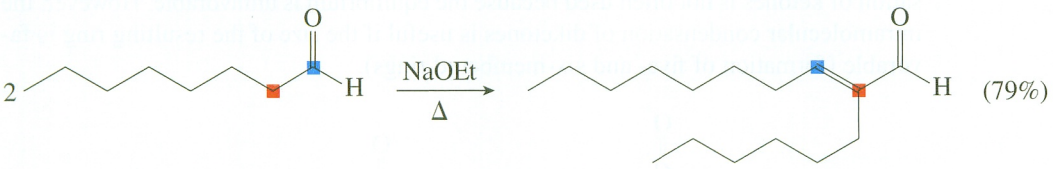
If the aldol condensation is conducted under more vigorous conditions (higher temperature, longer reaction time, and/or stronger base), elimination of water to form an α,β-unsaturated aldehyde usually occurs. This elimination is illustrated in the following example. Note that the α-carbon of one molecule is now doubly bonded to the carbonyl carbon of the other. (This text uses the symbol for heat, Δ, to indicate the vigorous conditions that cause eliminations to occur in these aldol condensations, even though other conditions might have been used.)



This elimination occurs by a somewhat different mechanism than those described in Chapter 9. Because the hydrogen on the α-carbon is relatively acidic, it is removed by the base in the first step to produce an enolate anion. Then hydroxide ion is lost from the enolate ion in the second step. Because this step is intramolecular and the product is stabilized by conjugation of its CC double bond with the CO double bond of the carbonyl group, even a poor leaving group such as hydroxide ion can leave. (This is an example of the E1cb mechanism described in the Focus On box on page 333 in Chapter 9.) Most aldol condensations are run under conditions that favor dehydration because the stability of the product helps drive the equilibrium in the desired direction, resulting in a higher yield. For example, the reaction of butanal shown previously results in a 75% yield of the aldol product. If the reaction is conducted so that dehydration occurs, the yield of the conjugated product is 97%.

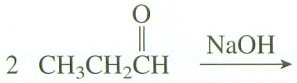


Another example is shown in the following equation:



PRACTICE PROBLEM 20.3

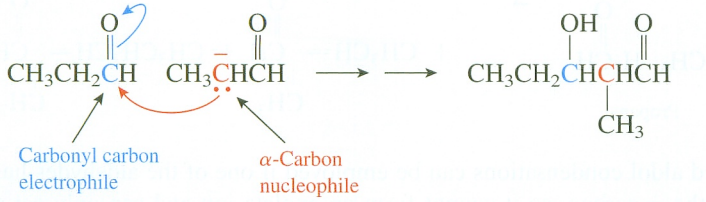
Show the product of this reaction:



Strategy

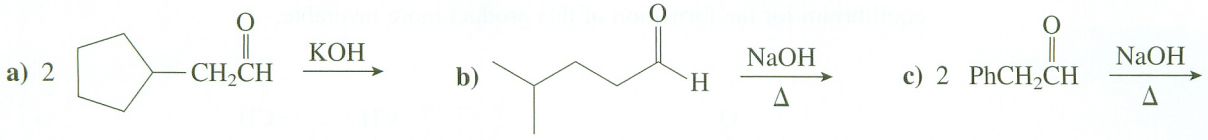
The key to determining the products of an aldol condensation is to remember that the nucleophile is an enolate anion, which is formed at the α-carbon of the aldehyde, and the electrophile is the carbonyl carbon of another aldehyde molecule. Therefore the product has the α-carbon of one aldehyde molecule bonded to the carbonyl carbon of another aldehyde molecule. Under milder conditions an OH group remains on the carbonyl carbon of the electrophile, whereas under vigorous conditions the α-carbon and the carbonyl carbon are connected by a double bond.

Solution



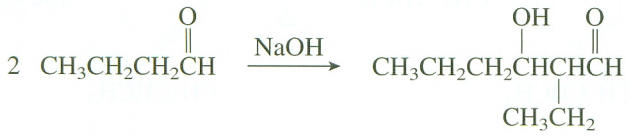
PROBLEM 20.9

Show the products of these reactions:

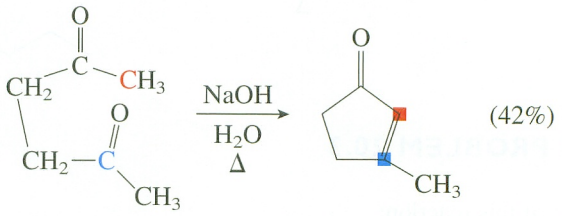


PROBLEM 20.10

Show all of the steps in the mechanism for this reaction:

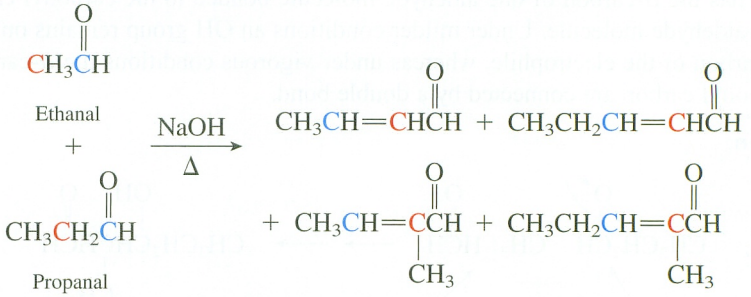


Ketones are less reactive electrophiles than aldehydes. Therefore, the aldol condensation of ketones is not often used because the equilibrium is unfavorable. However, the intramolecular condensation of diketones is useful if the size of the resulting ring is favorable (formation of five- and six-membered rings).

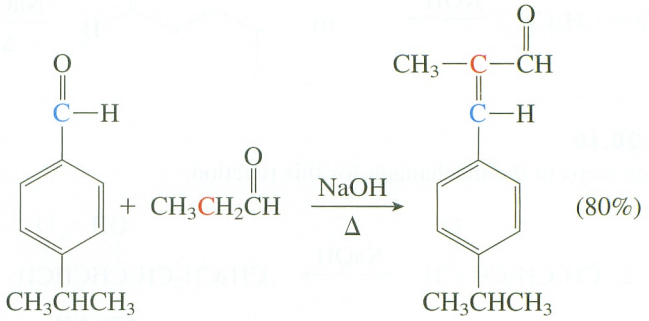


A diketone

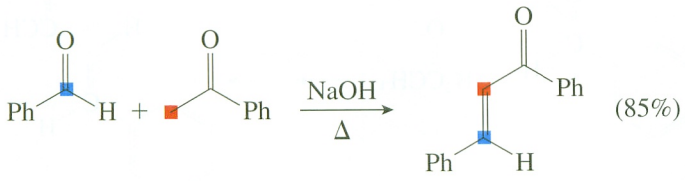
Often, it is desirable to conduct an aldol condensation in which the nucleophile and the electrophile are derived from different compounds. In general, such **mixed aldol condensations,** involving two different aldehydes, result in the formation of several products and for this reason are not useful. For example, the reaction of ethanal and propanal results in the formation of four products because there are two possible enolate nucleophiles and two carbonyl electrophiles:



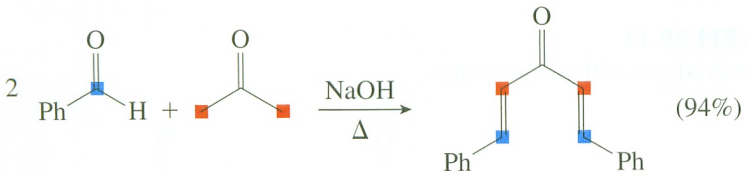
Mixed aldol condensations can be employed if one of the aldehydes has no hydrogens on the α-carbon, so it cannot form an enolate ion and can only act as the electrophilic partner in the reaction. Aromatic aldehydes are especially useful in this role because the dehydration product has additional stabilization from the conjugation of the newly formed CC double bond with the aromatic ring. This stabilization makes the equilibrium for the formation of this product more favorable.



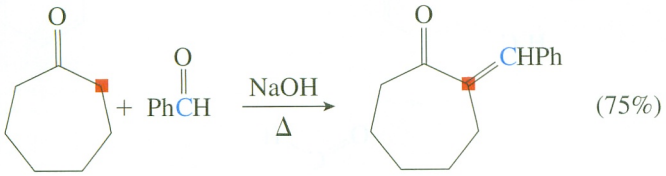
With an aromatic aldehyde as the electrophilic partner, the nucleophilic enolate ion can also be derived from a ketone or a nitrile. As illustrated in the following examples, this enables the aldol condensation to be used to form a wide variety of compounds:



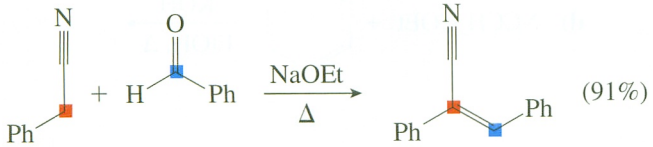
(85%)



(94%)



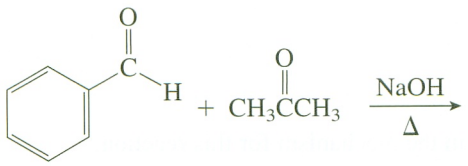
(75%)



(91%)

PRACTICE PROBLEM 20.4

Show the product of this reaction:

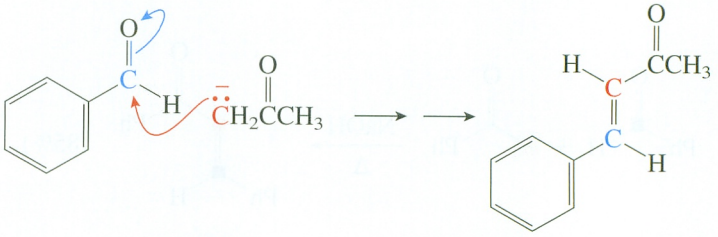


Strategy

Again, the key is to identify the nucleophile (the enolate anion) and the electrophile (the carbonyl carbon).

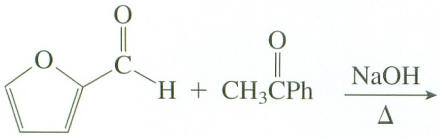
Solution

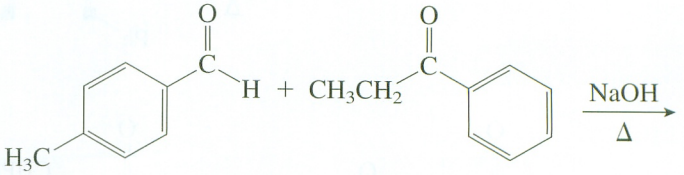
In this example the enolate anion can be derived only from acetone. The electrophile is the more reactive carbonyl carbon, that of benzaldehyde.

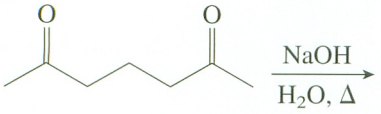


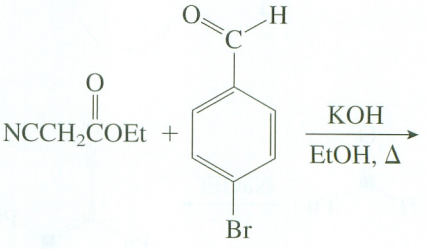
PROBLEM 20.11

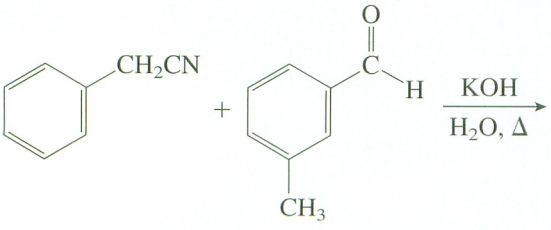
Show the products of these reactions:

a) 

b) 

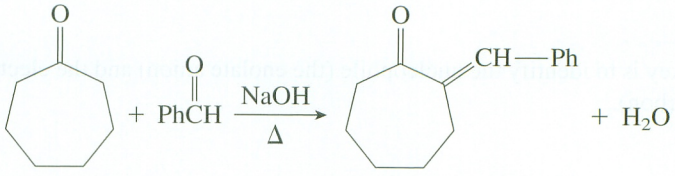
c) 

d) 

e) 

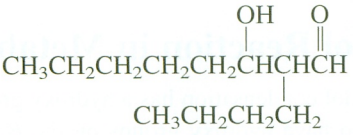
PROBLEM 20.12

Show all of the steps in the mechanism for this reaction:



PRACTICE PROBLEM 20.5

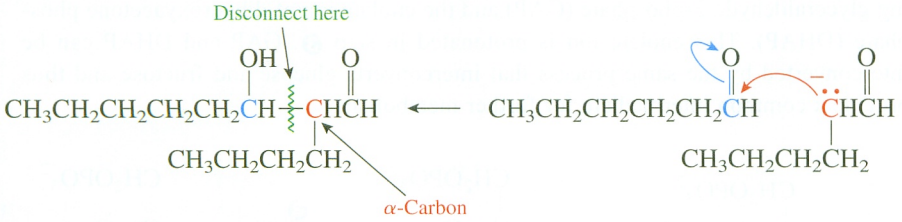
Show how the aldol condensation could be used to synthesize this compound:



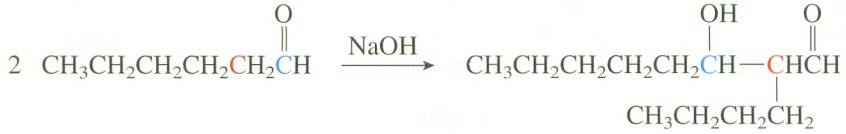
Strategy

First identify the carbon–carbon bond that could be formed in an aldol condensation. This is the bond between the α-carbon of the carbonyl group of the product and the carbon that is either doubly bonded to it or has a hydroxy substituent. Disconnection of this bond gives the fragments needed for the aldol condensation. Remember, the α-carbon of the product is the nucleophilic carbon of the enolate anion and the carbon to which it is bonded is the electrophilic carbonyl carbon.

Solution

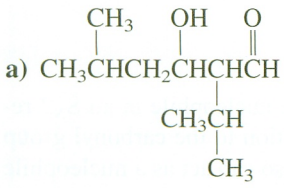


So the synthesis is

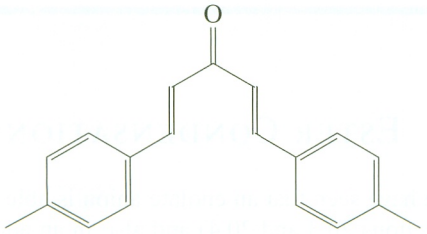


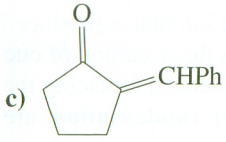
PROBLEM 20.13

Show how the aldol condensation could be used to synthesize these compounds.

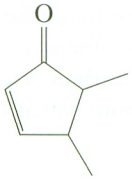


b)





d)



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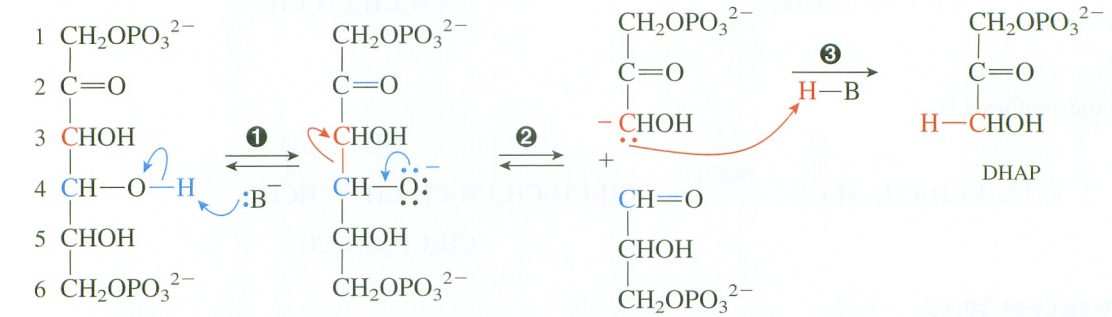
Click *Coached Tutorial Problems* to practice more **Aldol Condensations.**

Focus On Biological Chemistry

The Reverse Aldol Reaction in Metabolism

The initial product of an aldol condensation has a hydroxy group on the β-carbon to a carbonyl group. Sugars also have hydroxy groups on the β-carbon to their carbonyl groups, so they can be viewed as products of aldol condensations. In fact, a reverse aldol condensation is used in the metabolism of glucose (glycolysis) to cleave this six-carbon sugar into two three-carbon sugars.

To cleave a six-carbon sugar into two three-carbon fragments by a reverse aldol condensation, there must be a carbonyl group at C-2 and a hydroxy group at C-4. Therefore, glucose is first isomerized to fructose during its metabolism. The substrate for the cleavage reaction is the diphosphate ester, fructose-1,6-bisphosphate. In step ❶, a proton is removed from the hydroxy group on C-4. The bond between C-3 and C-4 is then broken in step ❷, which is the reverse of the aldol condensation, producing glyceraldehyde-3-phosphate (GAP) and the enolate ion of dihydroxyacetone phosphate (DHAP). This enolate ion is protonated in step ❸. GAP and DHAP can be interconverted by the same process that interconverts glucose and fructose and thus provide a common intermediate for further metabolism.

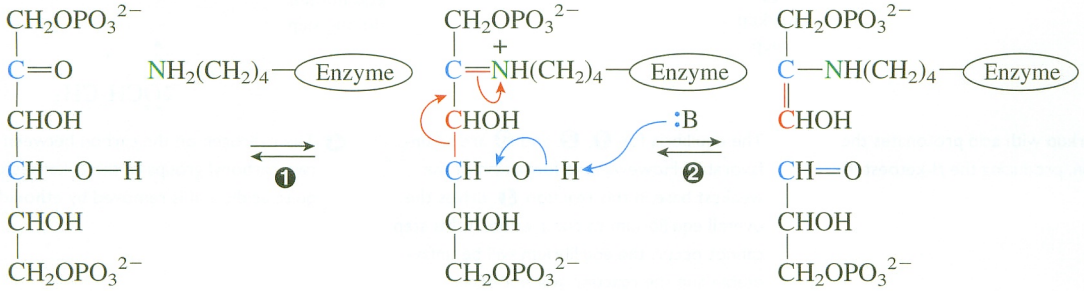


Fructose-1,6-bisphosphate GAP

20.6 Ester Condensations

So far, we have seen that an enolate anion is able to act as a nucleophile in an S_N2 reaction (Sections 20.3 and 20.4) and also in an addition reaction to the carbonyl group of an aldehyde in the aldol condensation (Section 20.5). It also can act as a nucleophile in a substitution reaction with the carbonyl group of an ester as the electrophile. When an ester is treated with a base such as sodium ethoxide, the enolate ion that is produced can react with another molecule of the same ester. The product has the α-carbon of one ester molecule bonded to the carbonyl carbon of a second ester molecule, replacing the alkoxy group. Examples of this reaction, called the **Claisen ester condensation,** are provided by the following equations:

The reverse aldol reaction is catalyzed by an enzyme called aldolase. One of the roles of the enzyme is to stabilize the enolate anion intermediate because such ions are too basic to be produced under physiological conditions. In animals, aldolase accomplishes this task by forming an imine bond between the carbonyl group of fructose-1,6-bisphosphate and the amino group of a lysine amino acid of the enzyme. As a result, the product of the reverse aldol step is an enamine derived from DHAP rather than its enolate anion. (Section 20.8 shows that enamines are the synthetic equivalents of enolate anions.) The formation of the strongly basic enolate anion is avoided. This process is outlined here:

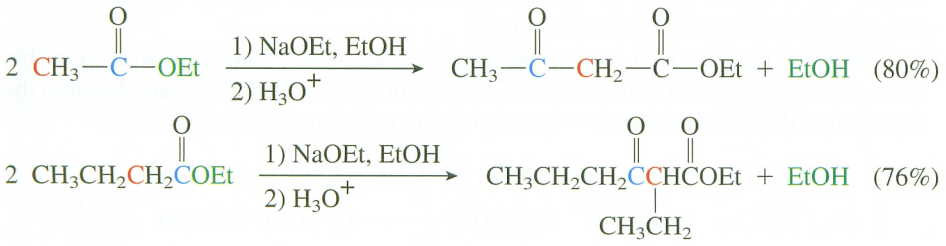


Fructose-1,6-bisphosphate

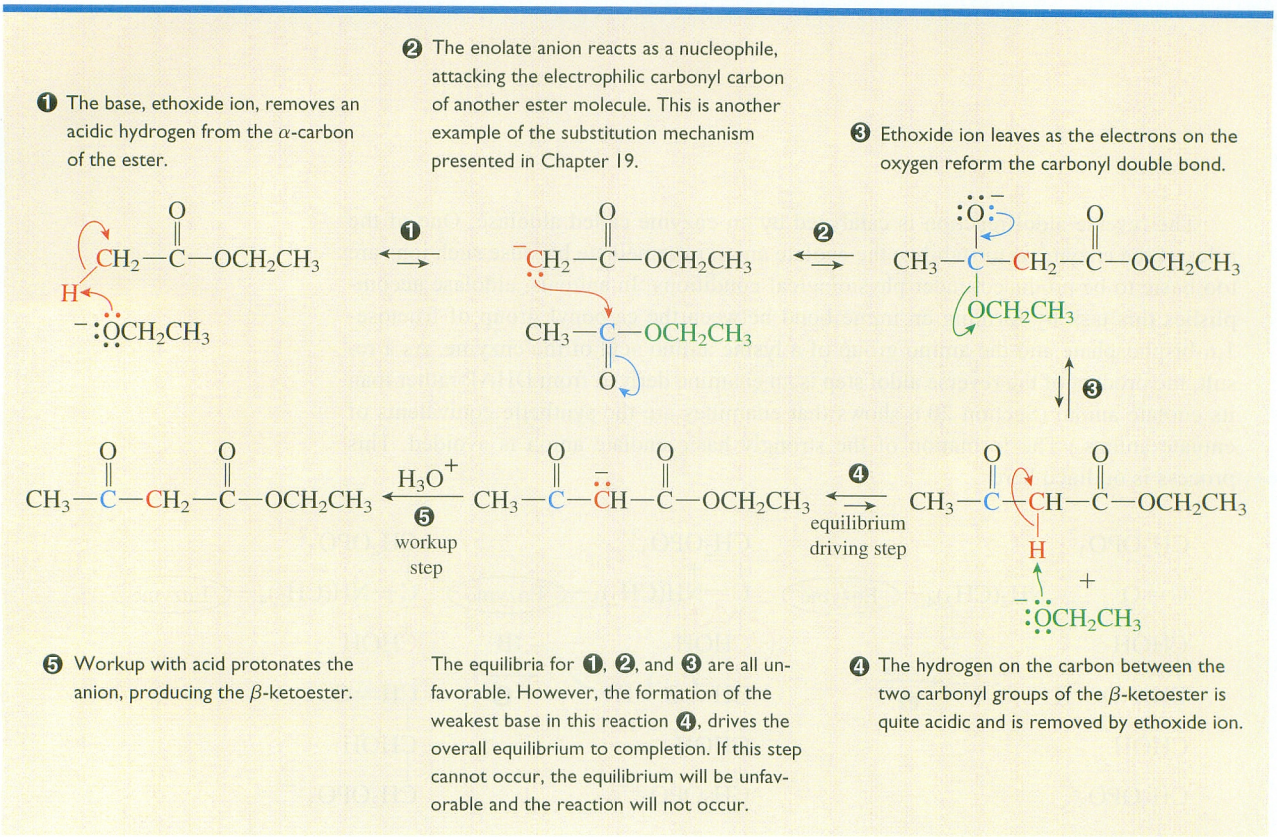
❶ An amino group of a lysine amino acid of the enzyme reacts with the carbonyl group of fructose-1,6-bisphosphate to form a protonated imine. See Figure 18.3 for the mechanism of this reaction.

❷ When the reverse aldol reaction occurs, an enamine, rather than a strongly basic enolate anion, is produced.

This enamine is hydrolyzed to DHAP, freeing the enzyme to catalyze another reverse aldol cleavage.



The mechanism for this reaction, shown in Figure 20.4, has similarities to those of both an aldol condensation (see Figure 20.3) and an ester saponification (see Figure 19.4). As was the case with the aldol condensation, the presence of both the enolate ion and the

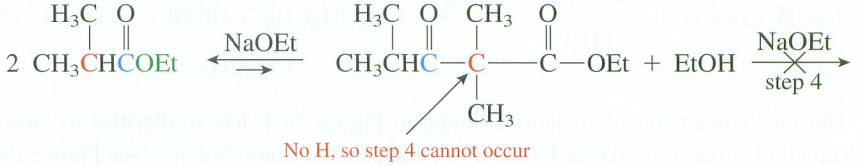


Active Figure 20.4 ORGANIC Chemistry Now™

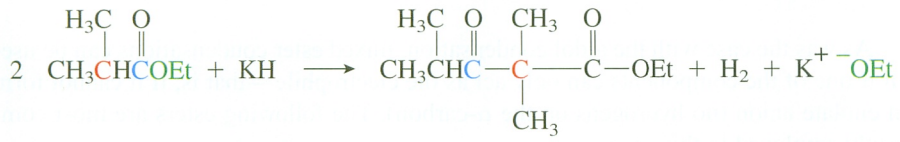
MECHANISM OF THE CLAISEN ESTER CONDENSATION. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

neutral ester is necessary for the reaction to occur. Therefore, ethoxide ion is used as the base because it is a weaker base than the enolate ion. Step 4 of the mechanism, in which ethoxide ion removes the acidic hydrogen, is of critical importance. The equilibria for the first three steps of the reaction are all unfavorable. But the equilibrium for step 4 is very favorable because the product of this step, the conjugate base of a β-ketoester, is the weakest base in the reaction. The formation of this weak base drives the equilibria to the product. If step 4 cannot occur, no significant amount of the β-ketoester is present in the reaction mixture and the condensation fails.

When sodium ethoxide is used as the base, the ester condensation fails with esters that have only one hydrogen on the α-carbon. The equilibrium favors the reactants because the equilibrium driving step (step 4 of the mechanism in Figure 20.4) cannot occur.

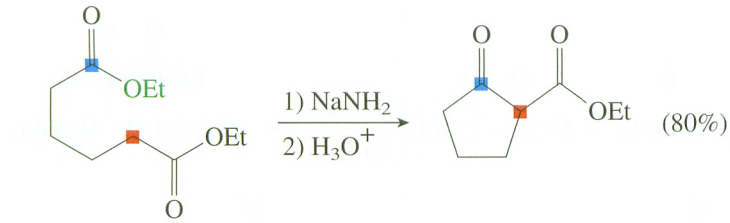


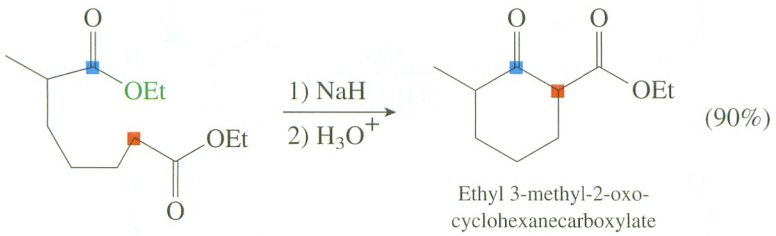
However, good yields of the condensation product can be obtained if a very strong base is used. In this case the equilibrium is driven toward the products because the ethoxide ion that is formed on the product side of the equation is weaker than the base on the reactant side of the equation. Note that only enough base is used to deprotonate one-half of the ester.



In fact, even with an ester that gives an acceptable yield of the condensation product with sodium ethoxide as the base, a better yield is often obtained when a stronger base is employed.

Intramolecular ester condensation reactions are called **Dieckmann condensations** and are very useful ring-forming reactions. Examples are shown in the following equations. In the second equation the yield is only 54% if sodium ethoxide is used as the base.

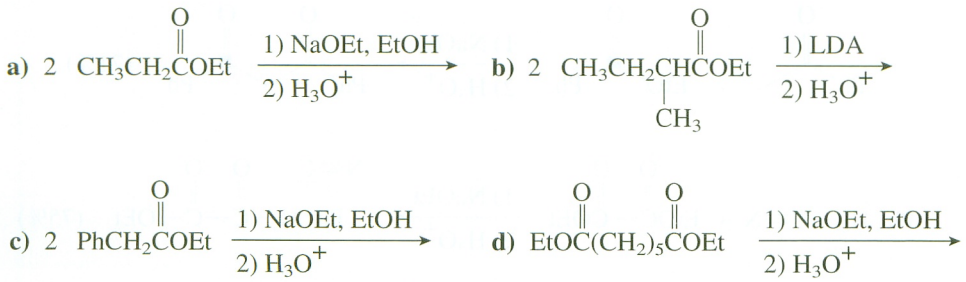




Ethyl 3-methyl-2-oxocyclohexanecarboxylate

PROBLEM 20.14

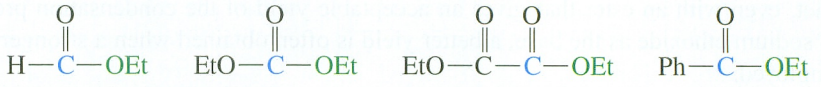
Show the products of these reactions:



PROBLEM 20.15

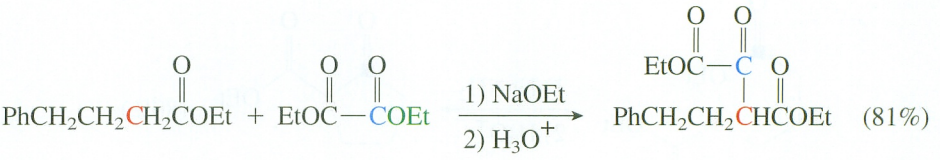
The second example of a Dieckmann condensation shown earlier produces ethyl 3-methyl-2-oxocyclohexanecarboxylate in 90% yield. What other cyclic product might have been formed in this reaction? Explain why the actual product is favored rather than this other product.

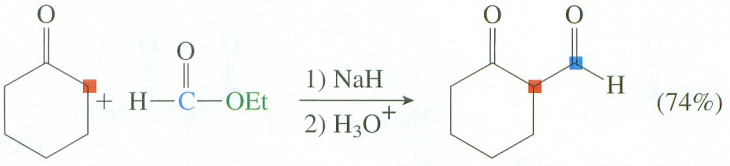
As was the case with the aldol condensation, mixed ester condensations can be useful if one of the components can only act as the electrophile—that is, if it cannot form an enolate anion (no hydrogens on the α-carbon). The following esters are most commonly employed in this role:

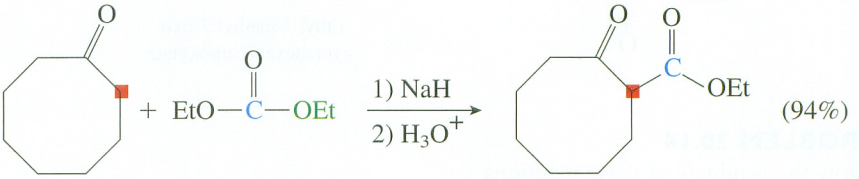


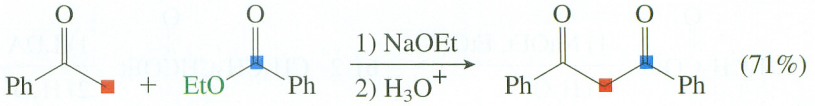
Ethyl formate | Diethyl carbonate | Diethyl oxalate | Ethyl benzoate

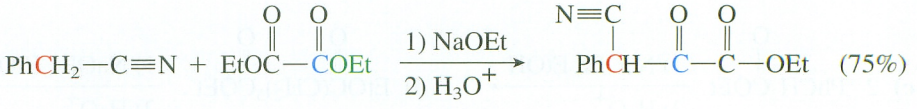
The nucleophile, an enolate or related anion, can be obtained by deprotonation of an ester, ketone, or nitrile. Examples are provided by the following equations:









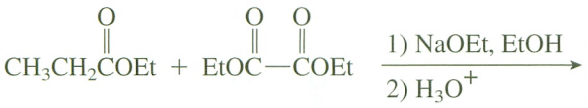


Finally, note that the products of most of these reactions are β-dicarbonyl compounds. They can be alkylated in the same manner as ethyl acetoacetate and diethyl

malonate, and they can also be decarboxylated if one of the two carbonyl groups is an ester group. This makes them quite useful in synthesis.

PRACTICE PROBLEM 20.6

Show the product of this reaction:



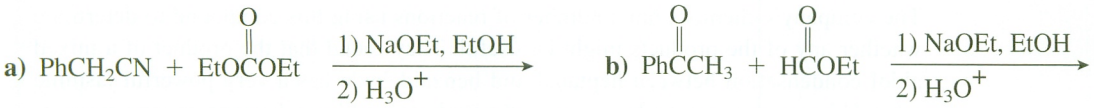
Strategy

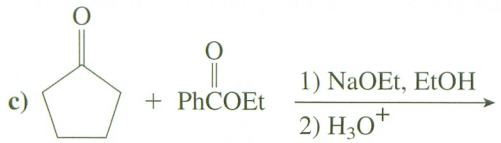
Again the best approach is to identify the site where the nucleophilic enolate anion forms, the α-carbon with the most acidic hydrogen. This carbon becomes bonded to the carbonyl carbon of the ester electrophile in the final product.

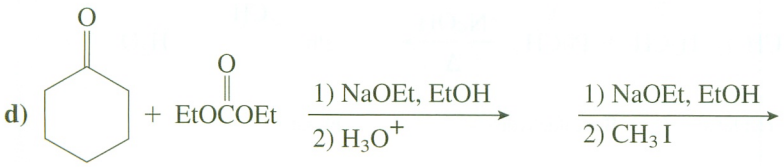
Solution

PROBLEM 20.16

Show the products of these reactions.

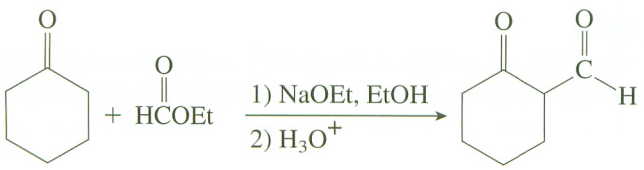






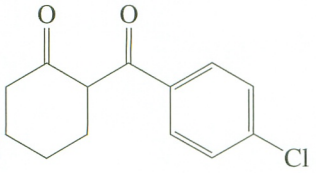
PROBLEM 20.17

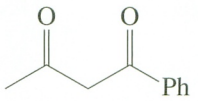
Show all of the steps in the mechanism for this reaction:

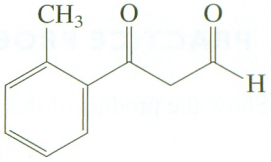


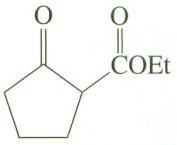
PROBLEM 20.18

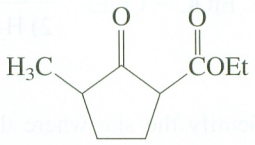
Show how ester condensation reactions could be used to synthesize these compounds:

a) 

b) 

c) 

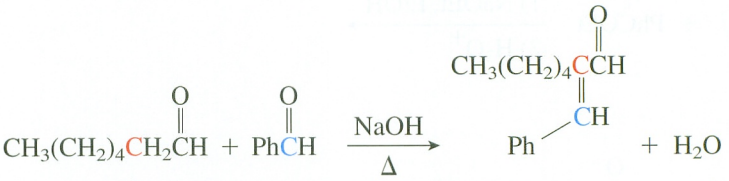
d) 

e) 

Focus On

An Industrial Aldol Reaction

The development of the perfumery ingredient Flosal, which has a strong jasminelike odor, provides an interesting example of how discoveries are sometimes made in an industrial setting. A chemical company was producing substantial amounts of heptanal as a by-product of one of its processes and needed to find some use for this aldehyde. The company's chemists ran a number of reactions using this compound to determine whether any of the products might be useful. They found that the product of a mixed aldol condensation between heptanal and benzaldehyde has a very powerful jasmine odor. This compound, which was given the trade name Flosal, became an important ingredient in soaps, perfumes, and cosmetics and was at one time prepared in amounts in excess of 100,000 pounds per year.



Heptanal Benzaldehyde Flosal

The synthesis must be carefully controlled to minimize the formation of the aldol product that results from the reaction of two molecules of heptanal (2-pentyl-2-nonenal) because this compound has an unpleasant, rancid odor.

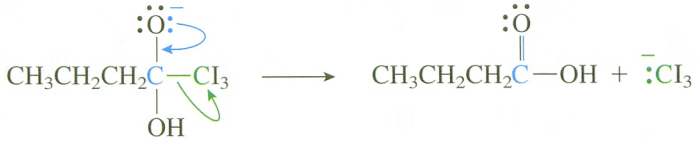
PROBLEM 20.19

Show the structure of the product of the aldol condensation of heptanal under vigorous conditions. How would you minimize the formation of this product in the synthesis of Flosal?

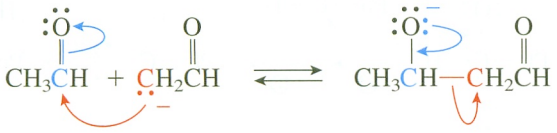
20.7 Carbon and Hydrogen Leaving Groups

Previously we learned that the carbonyl group of an aldehyde or a ketone does not undergo the substitution reactions of Chapter 19 because hydride ion and carbanions are strong bases and poor leaving groups. There are, however, some special situations in which these species do leave. Some of these exceptions are described in this section.

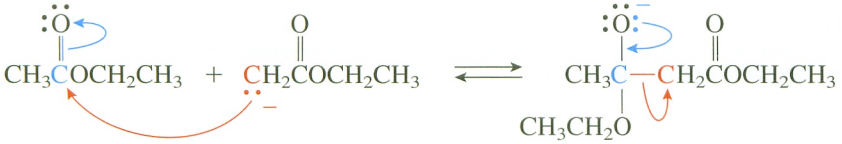
A carbanion can act as a leaving group if it is stabilized somehow. We have already seen several examples of this. For example, CX_3^-, a methyl carbanion stabilized by the inductive effect of three electronegative halogen atoms, leaves in the haloform reaction (see Section 20.2).



Another example is provided by the equilibrium in the aldol condensation. Examination of the mechanism for this reaction (see Figure 20.3) shows that an enolate anion leaves in the reverse of the second step of this reaction. Again, it is the stabilization of the carbanion, this time by resonance, that enables the enolate anion to leave.



A similar process is described in the Focus On box titled "The Reverse Aldol Reaction in Metabolism" on page 880. The Claisen ester condensation also has an equilibrium step in which an enolate anion leaves in the reverse of the step (see Figure 20.4).

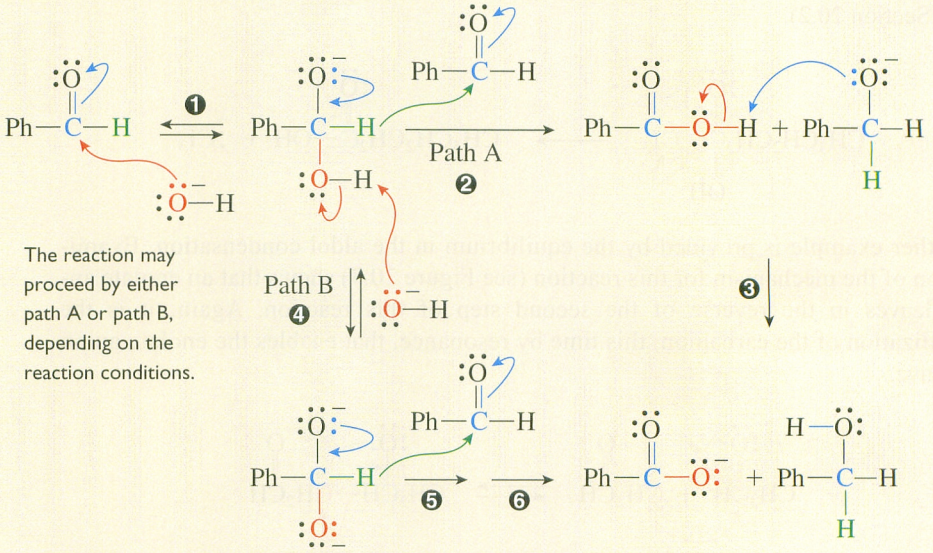


Reactions in which hydride leaves are less common but can occur if other reactions are precluded and the hydride is transferred directly to an electrophile. One example occurs when an aldehyde without any hydrogens on its α-carbon is treated with NaOH or KOH. (If the aldehyde has hydrogens on its α-carbon, the aldol condensation is faster and occurs instead.) In this reaction, called the Cannizzaro reaction, two molecules of aldehyde react. One is oxidized to a carboxylate anion and the other is reduced to a primary alcohol. The mechanism for this reaction is shown in Figure 20.5. The reaction begins in the same manner as the reactions described in Chapter 18; a hydroxide ion nucleophile attacks the carbonyl carbon of the aldehyde to form an anion. The reaction now begins to resemble the reactions in Chapter 19.

❶ The Cannizzaro reaction begins with the attack of the hydroxide ion nucleophile at the electrophilic carbon of the aldehyde, as described in Chapter 18.

❷ In path A, the electrons on the negative oxygen reform the double bond as hydride leaves. Hydride is too basic to leave by itself, so it is transferred to the electrophilic carbonyl carbon of another aldehyde molecule in a concerted step. This step is relatively slow and occurs only when no other reaction pathways, such as an aldol condensation, are available.

❸ An acid–base step completes the reaction.



❹ In path B, the initial anion loses a proton to the base, forming a dianion.

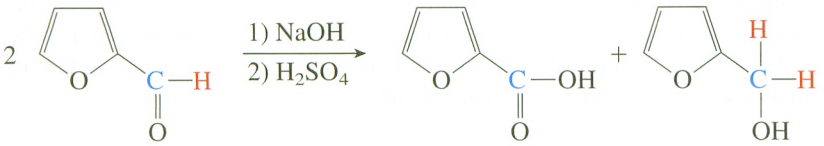
❺ Transfer of a hydride from the dianion to the second aldehyde molecule leads to the carboxylate anion and the conjugate base of the alcohol, ❻ which then obtains a proton from the solvent. Although the dianion is less stable than the initial anion, it is a stronger hydride donor because of its two negative charges.

Figure 20.5

MECHANISM OF THE CANNIZZARO REACTION.

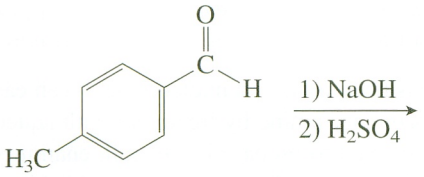
As the electrons on the negative oxygen reform the double bond, hydride ion begins to leave. But hydride ion is too poor a leaving group to leave without help, so it is transferred directly to the carbonyl carbon of a second aldehyde molecule, as shown in path A of the mechanism. An acid–base reaction completes the process. Under more strongly basic conditions, the mechanism may change slightly and follow path B. In this case the initially formed anion loses a proton to the base to form a dianion. Although the concentration of the dianion is less than that of the monoanion, it donates hydride more rapidly than the monoanion because of its two negative charges. After protonation of the alkoxide anion by the solvent, the same products are pro-

duced from path B as from path A. An example of the Cannizzaro reaction is provided in the following equation:



PROBLEM 20.20

Show the product of this reaction:



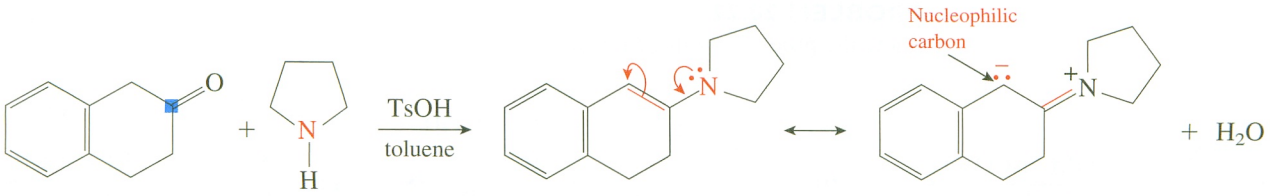
PROBLEM 20.21

β-Ketoesters that have two substituents on the α-carbon undergo fragmentation when treated with ethoxide anion as shown in the following equation. Suggest a mechanism for this reaction.

20.8 ENAMINES

Because of the importance of carbon nucleophiles in synthesis, organic chemists have spent considerable effort developing others in addition to the enolate anions that have already been described. Several of these other carbon nucleophiles are presented in this and the following section. This section describes the use of enamines.

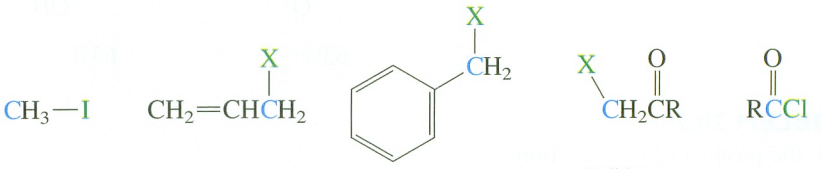
As discussed in Section 18.8, enamines are prepared by the reaction of a secondary amine with a ketone in the presence of an acid catalyst. The equilibrium is usually driven toward product formation by removal of water.



An enamine

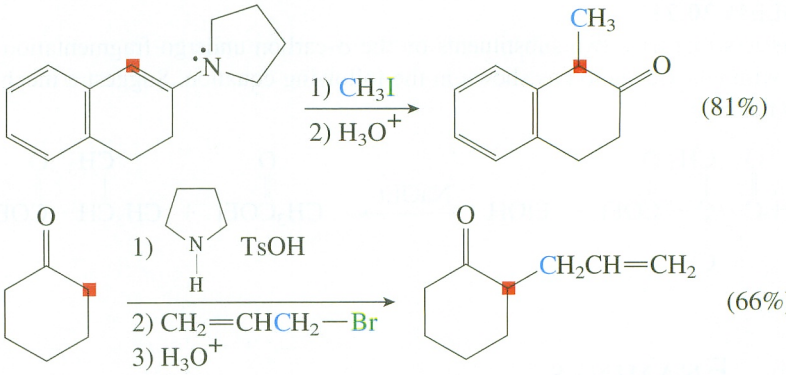
(93%)

Because of the contribution of structures such as the one on the right to the resonance hybrid, the α-carbon of an enamine is nucleophilic. However, an enamine is a much weaker nucleophile than an enolate anion. For it to react in the S_N2 reaction, the alkyl halide electrophile must be very reactive (see Table 8.1). An enamine can also be used as a nucleophile in substitution reactions with acyl chlorides. The reactive electrophiles commonly used in reactions with enamines are:



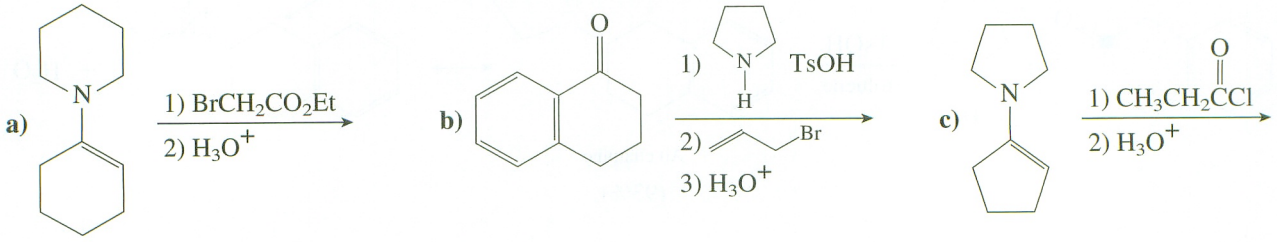
Methyl iodide | Allylic halides | Benzylic halides | Halides on α-carbons of ketones and esters | Acyl chlorides

After the enamine has been used as a nucleophile, it can easily be hydrolyzed back to the ketone and the secondary amine by treatment with aqueous acid. This is simply the reverse of the process used to prepare it. Overall, enamines serve as the synthetic equivalent of ketone enolate anions. Examples are provided in the following equations:



PROBLEM 20.22

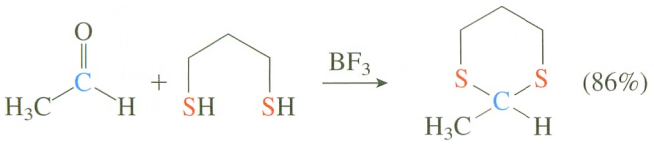
Show the products of these reactions:



20.9 Other Carbon Nucleophiles

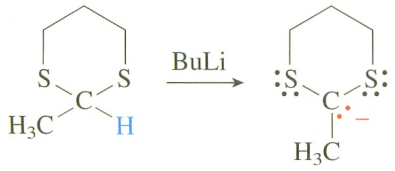
Many other carbon nucleophiles have been developed. Only two additional types are introduced here, but both provide interesting variations on the themes that have been presented so far.

The first of these nucleophiles is derived from a dithiane. A dithiane can be prepared by the reaction of an aldehyde with 1,3-propanedithiol. This reaction, described in Section 18.9, is the sulfur analog of acetal formation and requires a proton or Lewis acid catalyst:



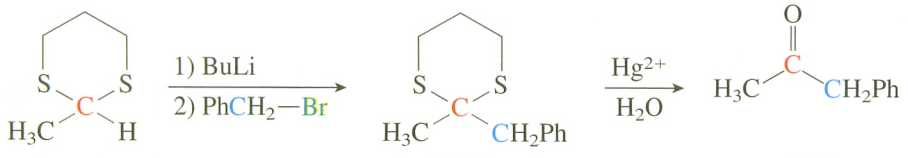
Acetaldehyde 1,3-Propanedithiol A dithiane

The hydrogen on the carbon attached to the two sulfur atoms is weakly acidic (pK_a = 31) and can be removed by reaction with a strong base, such as butyllithium. (Butyllithium is also a nucleophile, and therefore it is not used to generate enolate anions from carbonyl compounds. However, the dithiane is not electrophilic, so butyllithium can be used as the base in this reaction.)



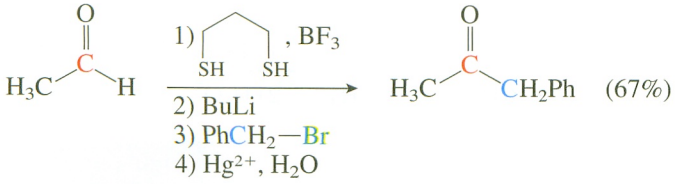
The acidity of the dithiane can be attributed to the stabilization of the conjugate base by the inductive effect of the sulfurs.

The dithiane anion is a good nucleophile in S_N2 reactions. After it has been alkylated, the thioacetal group can be removed by hydrolysis using Hg^{2+} as a Lewis acid catalyst.

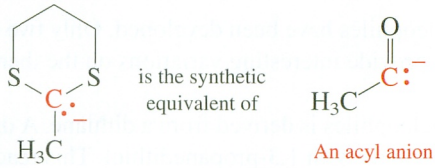


(98%) (80%)

The following equation provides an example of the overall process:

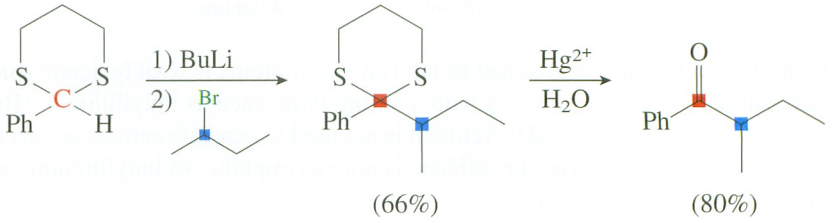


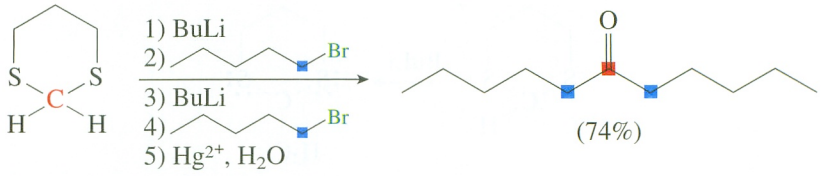
The nucleophile obtained by deprotonation of a dithiane serves as the synthetic equivalent of an acyl anion, a species that is too unstable to be prepared directly.



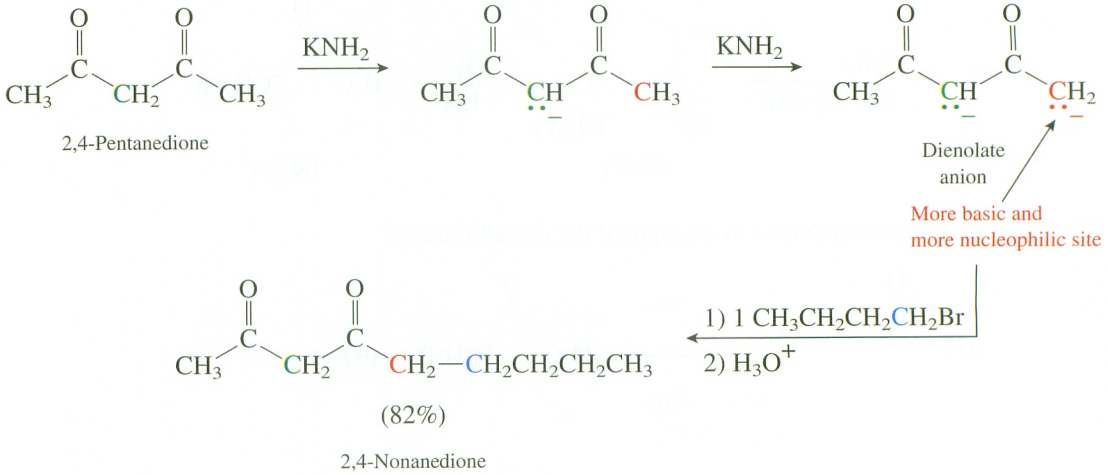
In all of the reactions that have been presented until this one, a carbonyl carbon has always reacted as an electrophile. An acyl anion, however, has a nucleophilic carbonyl carbon. Thus, the use of a nucleophile obtained by deprotonation of a dithiane provides an example of the formal reversal of the normal polarity of a functional group. Such **polarity reversal** is termed *umpolung,* using the German word for reversed polarity.

Additional examples of the use of a dithiane to generate an acyl anion synthetic equivalent are provided by the following equations:

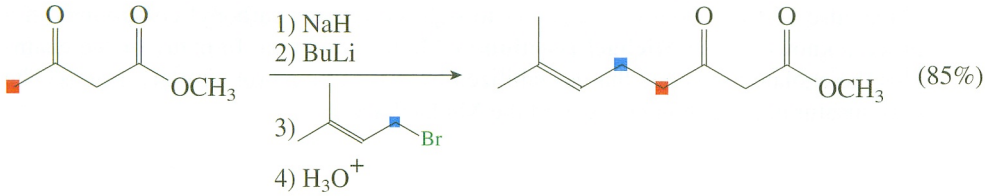




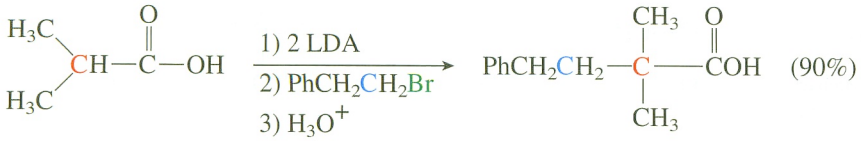
The final type of carbon nucleophile that is discussed in this chapter is a dianion. In some cases, treatment of an anion with a very strong base can remove a second proton to form a dianion. As an example, the reaction of 2,4-pentanedione with one equivalent of base removes a proton from the carbon between the two carbonyl groups. If this anion is treated with a second equivalent of a strong base, such as potassium amide, a second proton can be removed to form a dienolate anion:



When this dianion is reacted with one equivalent of an alkyl halide, the more basic site acts as a nucleophile. The addition of acid neutralizes the remaining anion. Overall, this process allows the more basic site to be alkylated preferentially. The following equation shows another example:

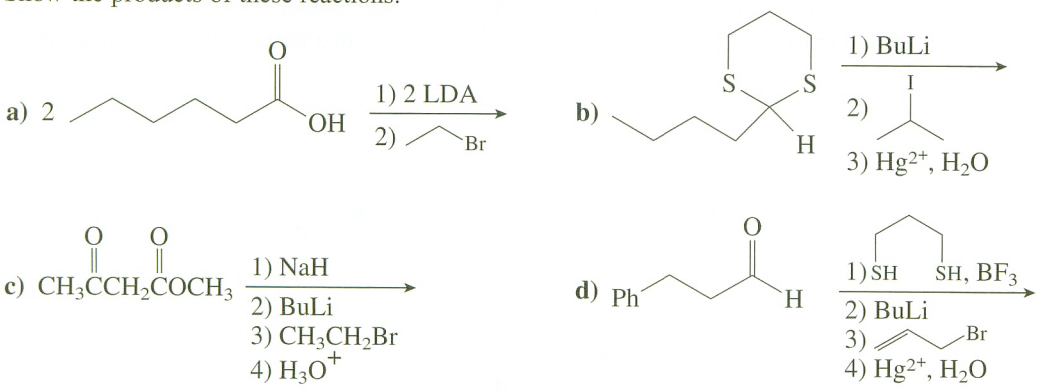


The same strategy can be extended to the alkylation of carboxylic acids at the α-carbon, as illustrated in the following example:



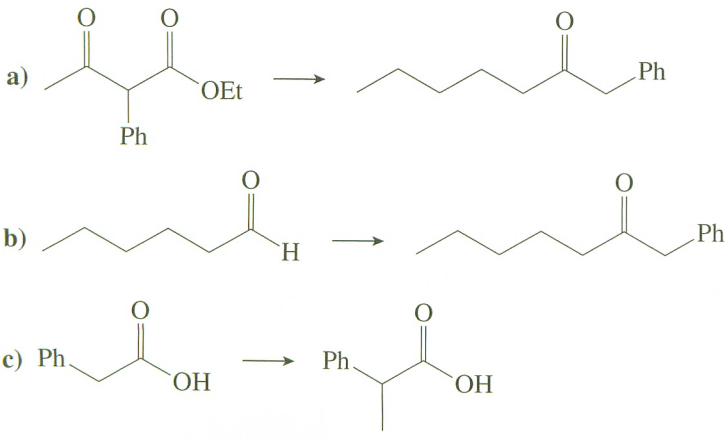
PROBLEM 20.23

Show the products of these reactions:



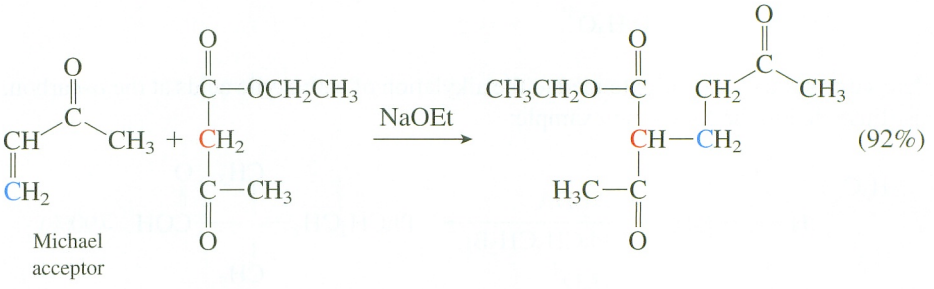
PROBLEM 20.24

Suggest methods to accomplish these transformations. More than one step may be necessary.

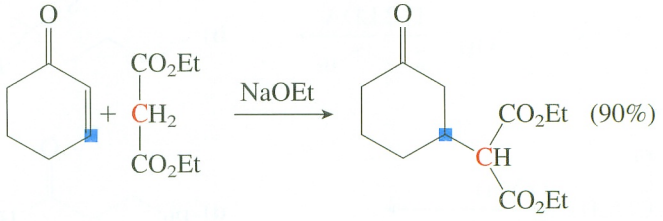


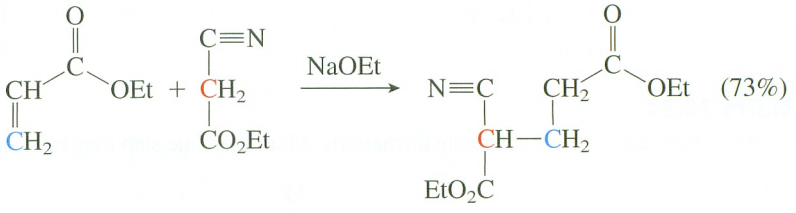
20.10 Conjugate Additions

The conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds at the β-position was described in Section 18.10. Enolate and related carbanion nucleophiles also add in a conjugate manner to α,β-unsaturated carbonyl compounds in a process known as the **Michael reaction** or Michael addition. In many of the examples the enolate ion is one that is stabilized by two carbonyl (or similar) groups. The α,β-unsaturated compound is called the Michael acceptor.



The mechanism for the Michael reaction is shown in Figure 20.6. Only a catalytic amount of base is needed because the initial adduct is itself an enolate anion and is basic enough to deprotonate the dicarbonyl compound, allowing additional reaction to occur. Other examples of the Michael reaction are provided in the following equations:





With stronger bases, less stable enolate anions can be generated and used in the Michael reaction:

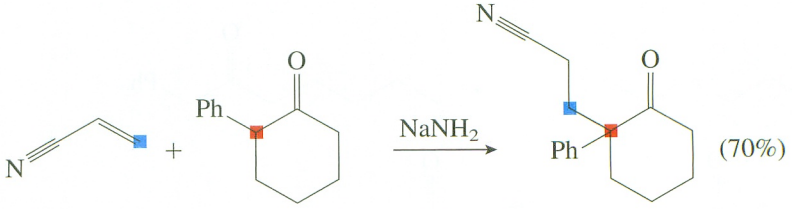
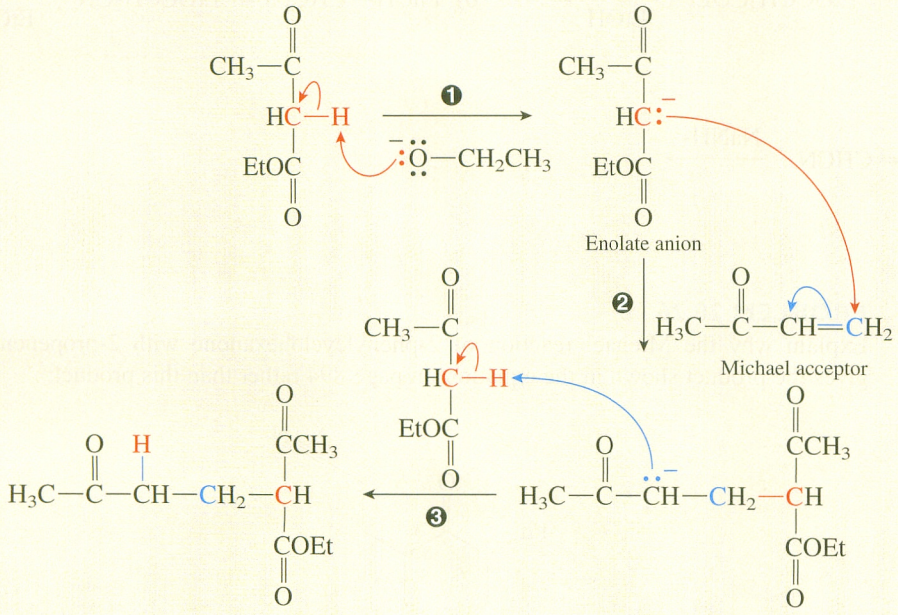


Figure 20.6

MECHANISM OF THE MICHAEL REACTION.

❶ The enolate anion of the β-dicarbonyl compound is generated in the usual manner.

❷ The enolate nucleophile adds to the β-carbon of an α,β-unsaturated ketone (or ester or nitrile), which is called the Michael acceptor.



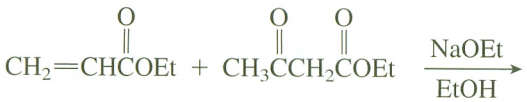
The product, formed in 92% yield in this case, has a bond from the α-carbon of the original enolate ion to the β-carbon of the Michael acceptor.

The product of this addition is an enolate ion.

❸ This ion reacts as a base with ethyl acetoacetate to regenerate another enolate ion, so only a catalytic amount of base is needed for the reaction.

PRACTICE PROBLEM 20.7

Show the product of this reaction:

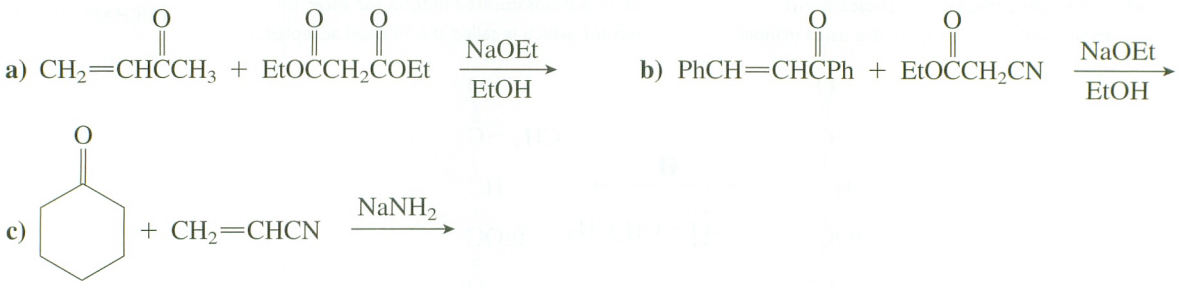


Solution

Identify the electrophile and the nucleophile. The base (NaOEt) removes the most acidic hydrogen, the one on the carbon between the carbonyl groups of ethyl acetoacetate, to generate the enolate anion. This nucleophile then attacks at the β-carbon of the Michael acceptor:

PROBLEM 20.25

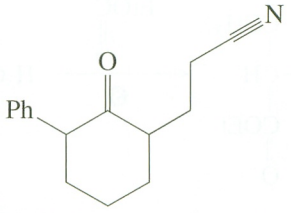
Show the products of these reactions:



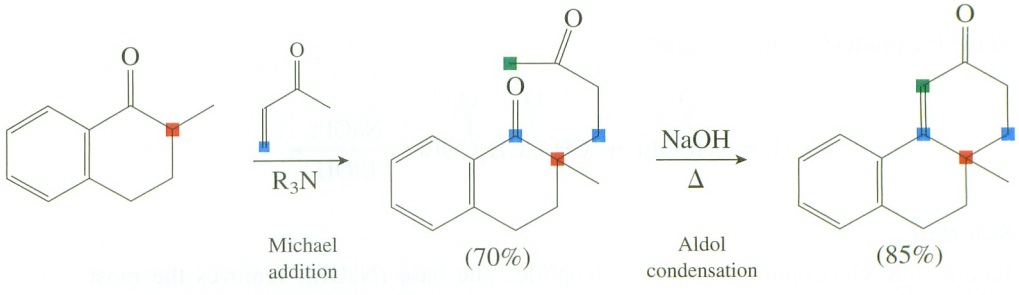
ORGANIC Chemistry Now™
Click *Coached Tutorial Problems* for more practice with the **Michael Reaction.**

PROBLEM 20.26

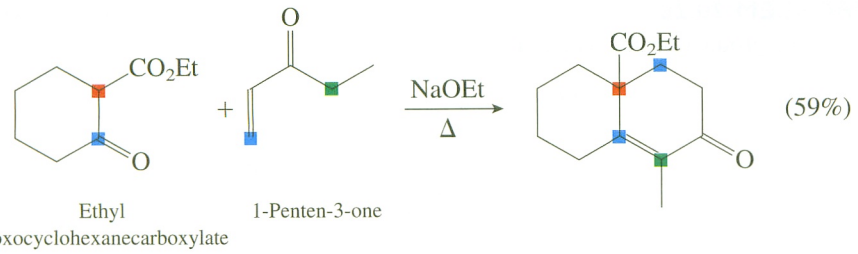
Explain why the Michael reaction of 2-phenylcyclohexanone with 2-propenenitrile gives the product shown in the equation on page 894 rather than this product:



The Michael reaction in combination with an aldol condensation provides a useful method for the construction of six-membered rings in a process termed the **Robinson annulation.** In the following example a tertiary amine is used as the base to catalyze the conjugate addition. Then, treatment with sodium hydroxide causes an intramolecular aldol condensation to occur.



Often, the Michael addition product is not isolated. Instead, the intramolecular aldol condensation occurs immediately, and the new six-membered ring is formed, as shown in the following equation. (However, when you are attempting to write the product of such a reaction, it is best to first write the product of Michael addition and then write the final product that results from the aldol condensation.)



Ethyl 2-oxocyclohexanecarboxylate

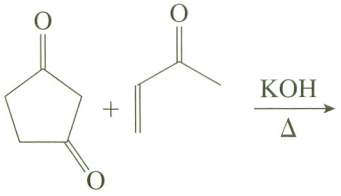
1-Penten-3-one

PROBLEM 20.27

Show the intermediate aldol product in the Robinson annulation reaction of ethyl 2-oxocyclohexanecarboxylate with 1-penten-3-one.

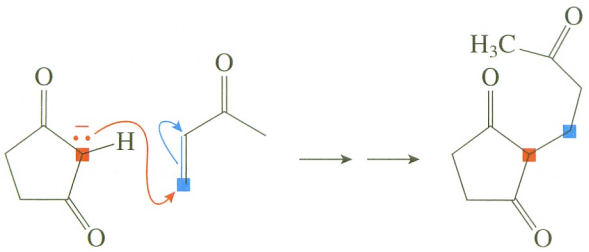
PRACTICE PROBLEM 20.8

Show the product of this Robinson annulation:

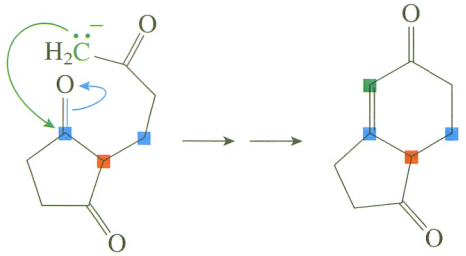


Solution

The base removes the most acidic hydrogen, and the resulting enolate anion undergoes a conjugate addition with the Michael acceptor:

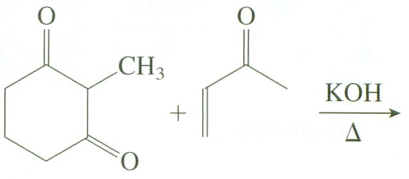


This product then undergoes an aldol condensation to give the final product:



PROBLEM 20.28

Show the product of this reaction:

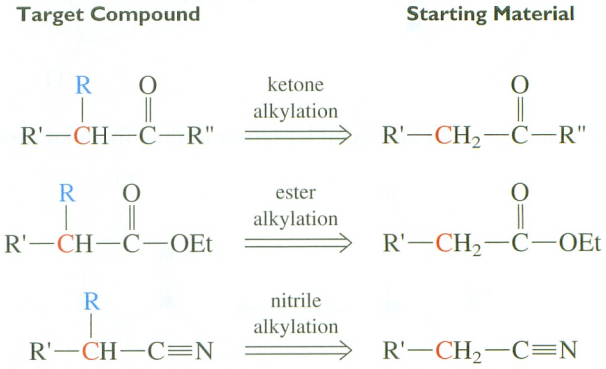


20.11 SYNTHESIS

The reactions presented in this chapter are very important in synthesis because they all result in the formation of carbon–carbon bonds. As we have seen, the best way to approach a synthesis problem is to employ retrosynthetic analysis, that is, to work backward from the target molecule to simpler compounds until a readily available starting material is reached. (Elias J. Corey, winner of the 1990 Nobel Prize in chemistry for "his development of the theory and methodology of organic synthesis," coined the term *retrosynthetic analysis* and formalized much of its logic. He also developed numerous new reagents, including the dithiane anion nucleophile discussed in Section 20.9, and synthesized a large number of natural products, including many prostaglandins [Section 28.9].) Recall that it is helpful in retrosynthetic analysis to recognize that certain structural features in the target suggest certain reactions. For example, we learned in Chapter 18 that an alcohol target compound suggests that a Grignard reaction might be used in its synthesis.

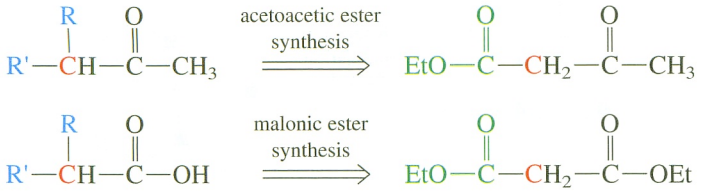
Let's look at the reactions presented in this chapter in terms of their products so that we might more easily recognize the synthetic reactions that are suggested by the presence of certain features in the target compound.

Alkylations of ketones, esters, and nitriles add an alkyl group to the α-carbon of compounds containing these functional groups. Therefore, a target molecule that is a ketone, ester, or nitrile with an alkyl group(s) attached to its α-carbon suggests the use of one of these alkylation reactions, as illustrated in the following equations using retrosynthetic arrows:

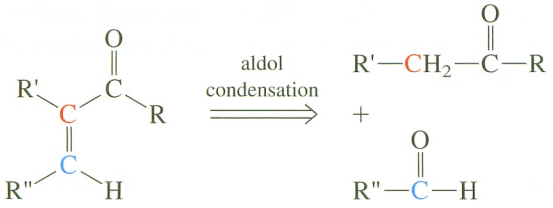


The acetoacetic ester synthesis produces a methyl ketone with an alkyl group(s) substituted on the α-carbon, whereas the malonic ester synthesis produces a

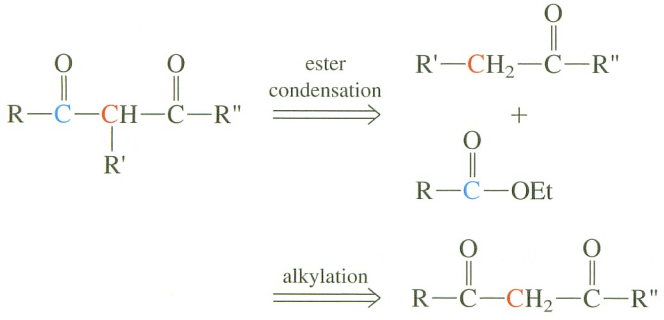
carboxylic acid with an alkyl group(s) substituted on the α-carbon. Note that these targets can sometimes also be synthesized by the direct alkylation of a ketone or ester:



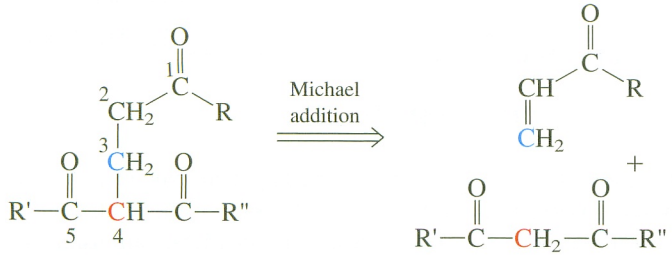
The presence of a carbon–carbon double bond conjugated to a carbonyl group (an α,β-unsaturated aldehyde, ketone, and so on) in the target compound suggests that an aldol condensation be employed:



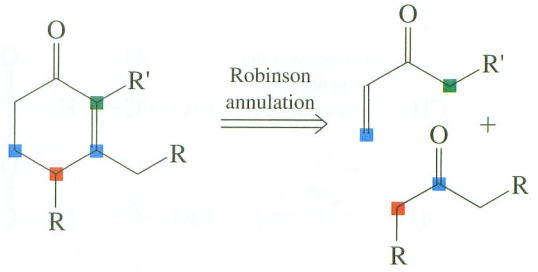
If the target compound has two carbonyl groups attached to the same carbon, an ester condensation is suggested. Note that such a target could also be prepared by alkylation of a β-dicarbonyl compound:



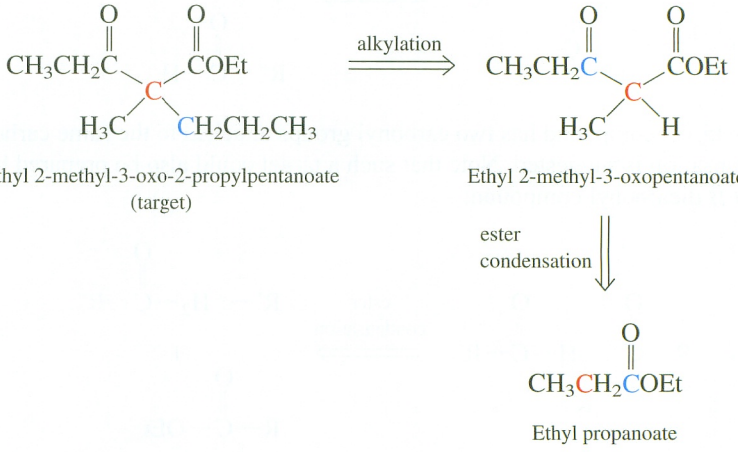
The presence of two carbonyl groups (or other functional groups that are capable of stabilizing a carbanion) in a 1,5-relationship suggests the use of a Michael addition to prepare that target compound:



Finally, the presence of a cyclohexenone ring in the target suggests that a Robinson annulation might be employed in its synthesis:



Let's try a synthesis. Suppose the target is ethyl 2-methyl-3-oxo-2-propylpentanoate. The presence of the β-ketoester functionality suggests employing an alkylation reaction and/or an ester condensation. In one potential pathway, the propyl group can be attached by alkylation of a simpler β-ketoester. Further retrosynthetic analysis suggests that the new target (ethyl 2-methyl-3-oxopentanoate) can be prepared from ethyl propanoate by a Claisen ester condensation.

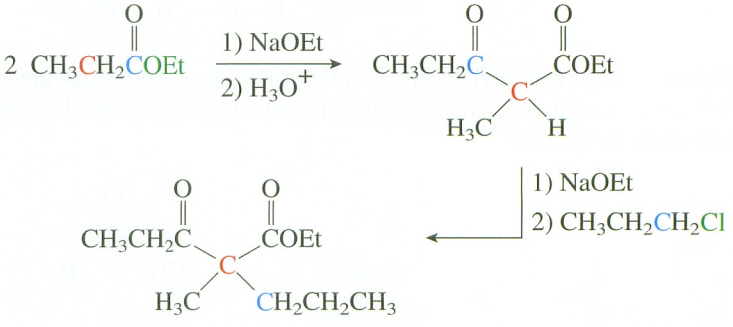


Ethyl 2-methyl-3-oxo-2-propylpentanoate (target)

Ethyl 2-methyl-3-oxopentanoate

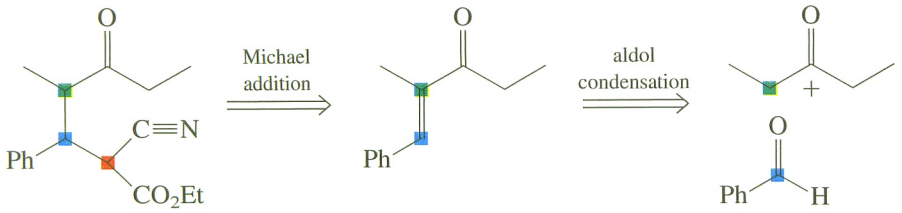
Ethyl propanoate

Written in the forward direction, the synthesis is



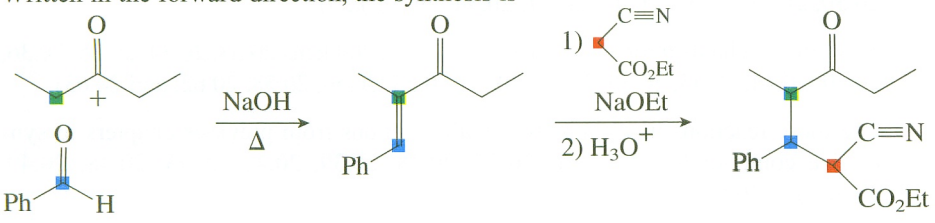
As another example, consider the following target compound. A Michael reaction is suggested by the observation that the carbonyl group of the ketone and the ester carbonyl group (or the carbon of the cyano group) are in a 1,5-relationship. The compound

required for the Michael addition is an α,β-unsaturated ketone, suggesting that a mixed aldol condensation be used to prepare it.



Target

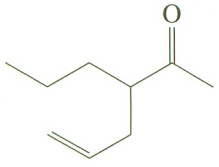
Written in the forward direction, the synthesis is



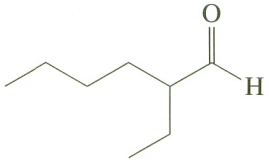
Like any other endeavor, the only way to become proficient in designing syntheses is practice. Work the problems and, when working them, examine each target compound for structural features that suggest certain reactions. Remember that most targets can be reached by numerous pathways, so if your route does not match the one presented in the answers, do not despair. Check all of the reactions that you use to ensure that they are appropriate. If your pathway seems a reasonable route to the target, then it may be as good as, or even better than, the one shown in the answer.

PROBLEM 20.29

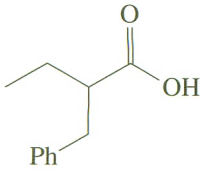
Show syntheses of these compounds from the indicated starting materials:

a) 

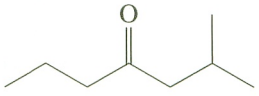
from ethyl acetoacetate

b) 

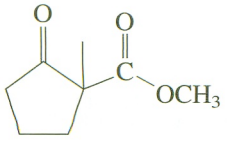
from butanal

c) 

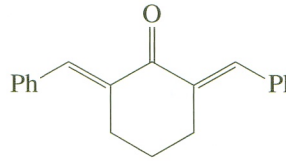
from ethyl butanoate

d) 

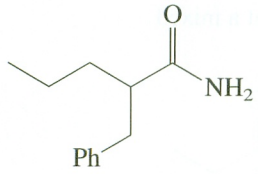
from butanal

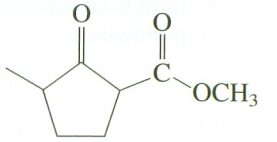
e) 

from cyclopentanone

f) 

from cyclohexanone

g)  from diethyl malonate

h)  from cyclopentanone

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Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the products of any of the reactions discussed in this chapter. (Problems 20.30, 20.31, 20.32, 20.41, 20.47, 20.54, and 20.55)
- Show the mechanism for any of these reactions. (Problems 20.33, 20.34, 20.35, 20.36, 20.40, 20.44, 20.45, 20.46, 20.51, 20.52, 20.53, 20.56, 20.58, 20.62, and 20.63)
- Use these reactions in combination with reactions from previous chapters to synthesize compounds. (Problems 20.37, 20.38, 20.39, 20.42, 20.43, 20.48, 20.49, 20.50, and 20.57)

Visual Summary of Key Reactions

A large number of reactions have been presented in this chapter. However, all of these reactions involve an enolate ion (or a related species) acting as a nucleophile (see Table 20.2). This nucleophile reacts with one of the electrophiles discussed in Chapters 8, 18, and 19 (see Table 20.3). The nucleophile can bond to the electrophilic carbon of an alkyl halide (or sulfonate ester) in an S_N2 reaction, to the electrophilic carbonyl carbon of an aldehyde or ketone in an addition reaction (an aldol condensation), to the electrophilic carbonyl carbon of an ester in an addition reaction (an ester condensation) or to the electrophilic β-carbon of an α,β-unsaturated compound in a conjugate addition (Michael reaction). These possibilities are summarized in the following equations:

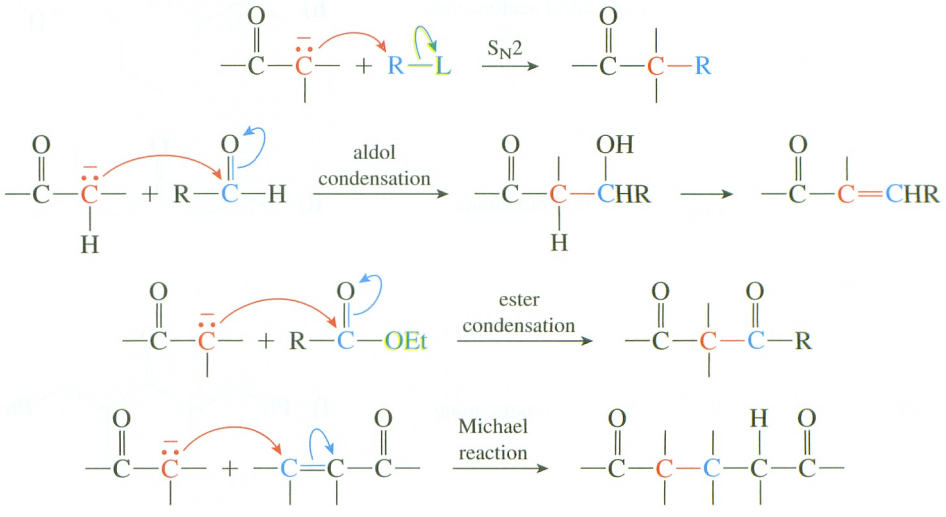


Table 20.2 Carbon Nucleophiles

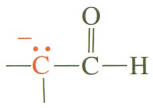
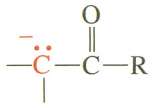
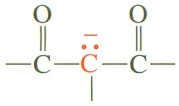
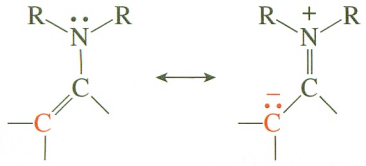
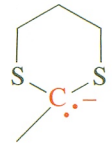
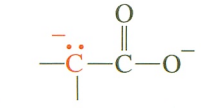
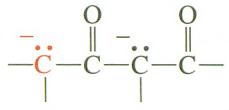
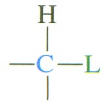
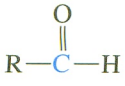
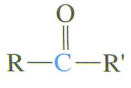
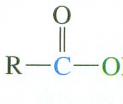
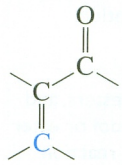
Nucleophile	Comments
	Because aldehydes are so reactive as electrophiles, enolate anions derived from them are primarily restricted to use in the aldol condensation.
	Enolate anions derived from ketones, esters, and nitriles can be alkylated, used in the aldol or ester condensations, or used in the Michael reaction.
	Enolate anions that are stabilized by two carbonyl groups (or cyano groups) can be alkylated and give excellent yields in the Michael reaction.
	Enamines react only with very reactive electrophiles.
	Dithiane anions are acyl anion equivalents and can be readily alkylated.
 	These dianions can be selectively alkylated at the more basic site.

Table 20.3 Electrophiles

Electrophiles	Comments
	The carbon must be primary or secondary to use these compounds in an S_N2 reaction. The leaving group can be a halide or a sulfonate group.
	Aldehydes are very reactive electrophiles in the aldol condensation.
	Ketones are less reactive and are most useful when the aldol condensation is intramolecular.

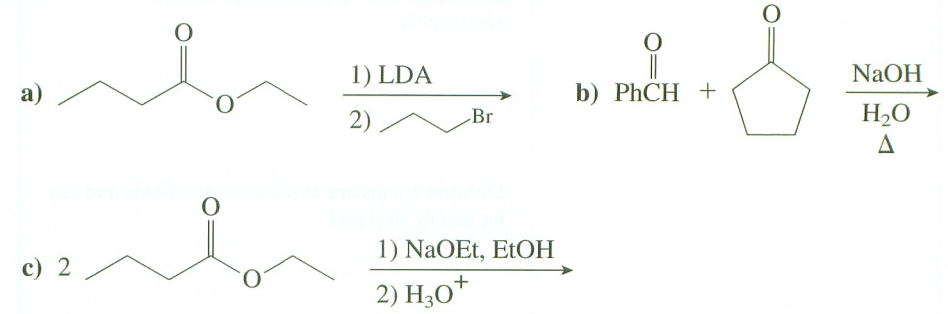
Continued

Table 20.3 Electrophiles—cont'd

Electrophiles	Comments
	Esters are useful in the Claisen ester condensation. Most often, R′ = Me or Et.
	α,β-Unsaturated compounds are useful in the Michael reaction. A cyano group can be used in place of the carbonyl group.

Integrated Practice Problem

Show the products of these reactions:

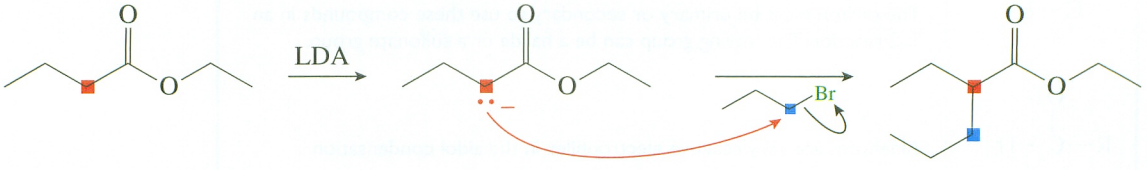


Strategy

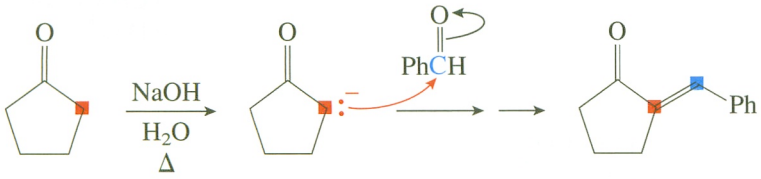
Students often have difficulty with these reactions because the products are large and rather complex. You will have a much easier time remembering these reactions if you first identify the site where the enolate anion or related nucleophile will form (Table 20.2) and then identify the electrophilic site (Table 20.3). The product simply results from bonding the nucleophilic carbon to the electrophilic carbon.

Solutions

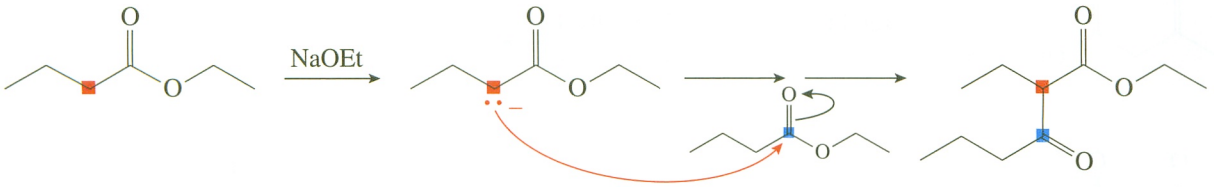
a) LDA is a strong base and removes a proton from the α-carbon of the ester. The resulting enolate anion acts as a nucleophile in an S_N2 reaction with the alkyl bromide.



b) The base removes the acidic hydrogen on the α-carbon of cyclopentanone. The resulting enolate anion nucleophile bonds to the electrophilic carbonyl carbon of benzaldehyde in an aldol condensation.



c) The base removes the acidic hydrogen on the α-carbon of the ester. The resulting enolate anion nucleophile bonds to the electrophilic carbonyl carbon of another ester molecule in an ester condensation.



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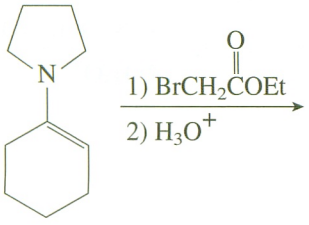
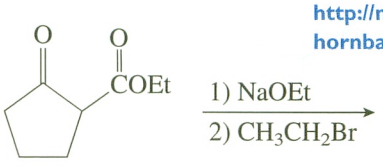
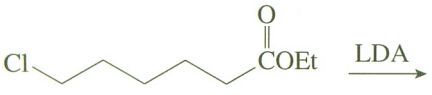
Assess your understanding of this chapter's topics with additional quizzing and conceptual-based problems at **http://now.brookscole.com/hornback2**

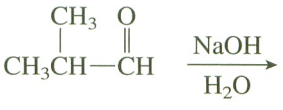
Additional Problems

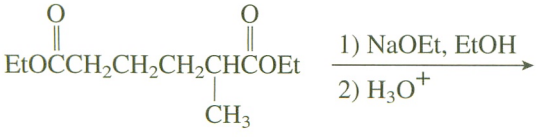
20.30 Show the products of these reactions:

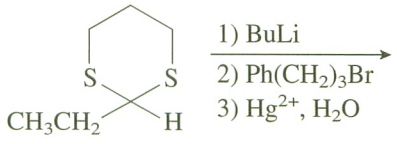
a) 

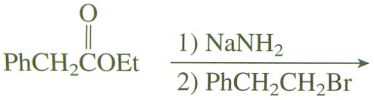
b) 

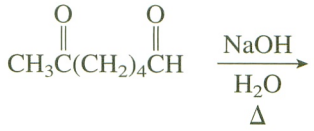
c) 

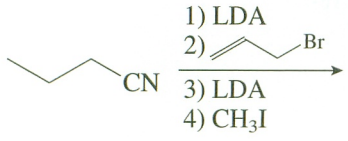
d) 

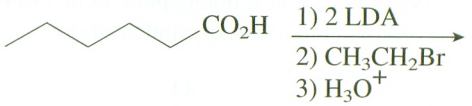
e) 

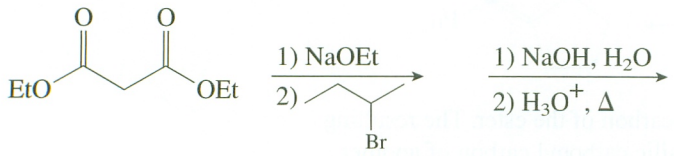
f) 

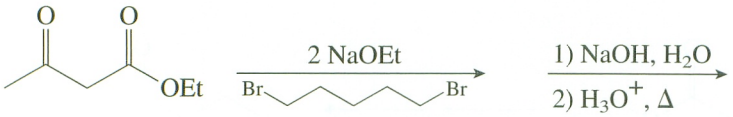
g) 

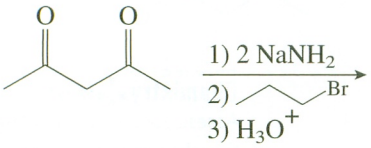
h) 

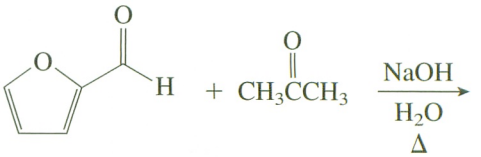
i) 

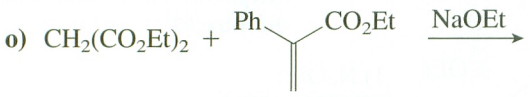
j) 

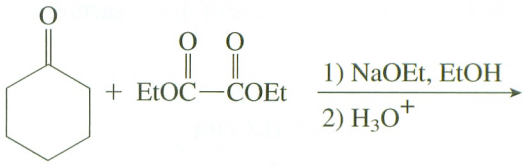
k) 

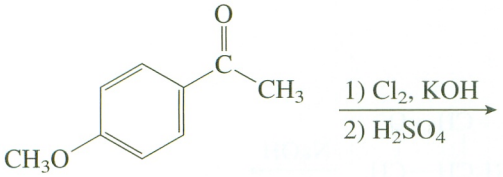
l) 

m) 

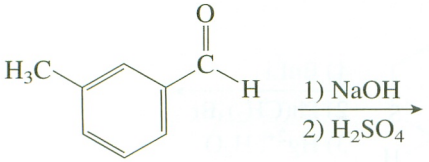
n) 

o) 

p) 

q) 

r) 

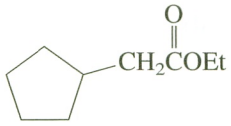
s) 

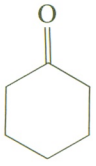
20.31 Show the products of these reactions:

a) $CH_3CH_2CH_2CN$ $\xrightarrow[2)\ CH_3CH_2Br]{1)\ LDA}$

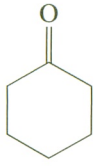
b) $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow[2)\ CH_3\underset{CH_3}{\underset{|}{C}}HCH_2Br]{1)\ NaOEt,\ EtOH}$ $\xrightarrow[2)\ H_3O^+,\ \Delta]{1)\ NaOH,\ H_2O}$

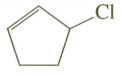
c) 2 $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H$ $\xrightarrow[\Delta]{\substack{NaOH\\H_2O}}$

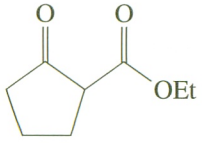
d) 2  $\xrightarrow[2)\ H_3O^+]{1)\ NaOEt,\ EtOH}$

e)  $\xrightarrow[2)\ PhC\overset{O}{\overset{\|}{C}}Cl\\3)\ H_3O^+]{1)\  TsOH}$

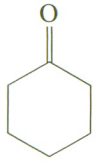
f) $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow[2)\ BuLi\\3)\ PhCH_2Br\\4)\ H_3O^+]{1)\ NaH}$

g)  + $EtO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow[\Delta]{NaOEt}$

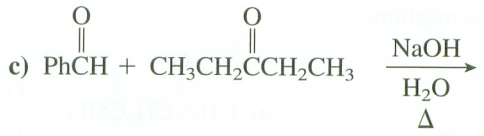
h) $EtO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow[2)\ ]{1)\ NaOEt,\ EtOH}$

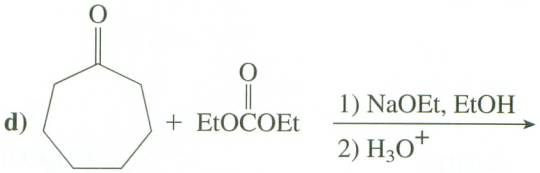
i)  $\xrightarrow[2)\ CH_3I]{1)\ NaOEt,\ EtOH}$ $\xrightarrow[2)\ H_3O^+,\ \Delta]{1)\ NaOH,\ H_2O}$

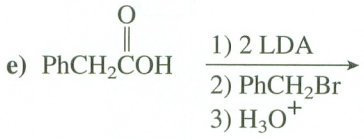
20.32 Show the products of these reactions:

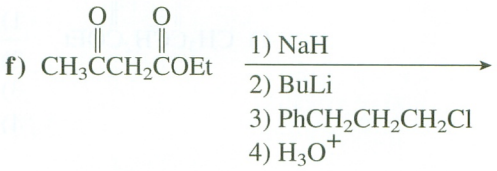
a)  $\xrightarrow[2)\ PhCH_2Br]{1)\ LDA}$

b) $EtO\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OEt$ $\xrightarrow[CH_3I\ (excess)]{NaOEt\ (excess)}$ $\xrightarrow[2)\ H_3O^+,\ \Delta]{1)\ NaOH,\ H_2O}$

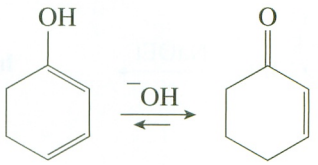




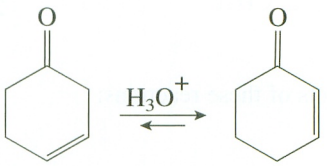




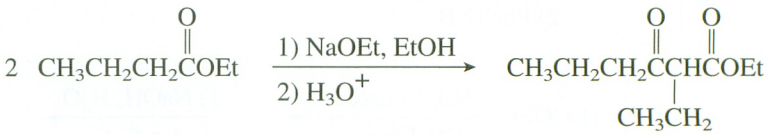
20.33 Suggest a mechanism for this reaction:



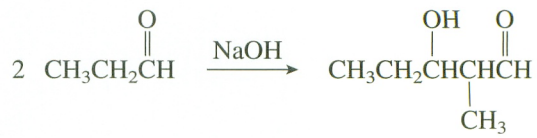
20.34 Suggest a mechanism for this reaction. (The reaction does not occur by a carbocation rearrangement.)



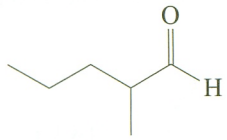
20.35 Show all of the steps in the mechanism for this reaction:

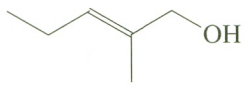


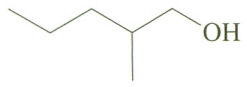
20.36 Show all of the steps in the mechanism for this reaction:

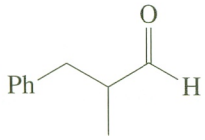


20.37 Show syntheses of these compounds from propanal:

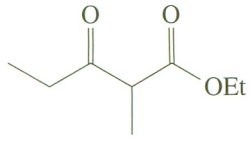
a) 

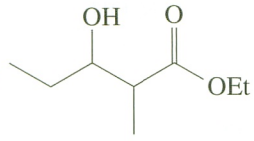
b) 

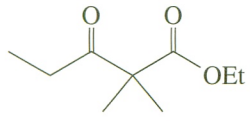
c) 

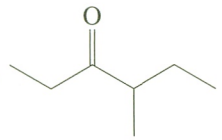
d) 

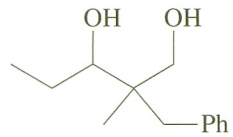
20.38 Show syntheses of these compounds from ethyl propanoate:

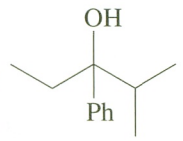
a) 

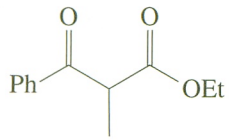
b) 

c) 

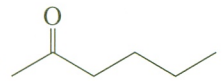
d) 

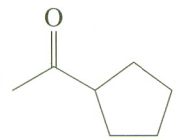
e) 

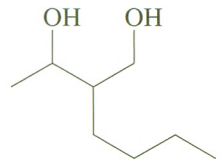
f) 

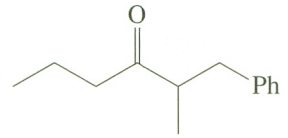
g) 

20.39 Show syntheses of these compounds from ethyl acetoacetate:

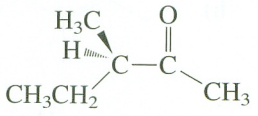
a) 

b) 

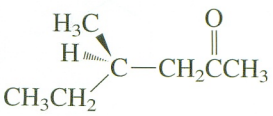
c) 

d) 

20.40 Optically active ketone **A** undergoes racemization in basic solution. Show a mechanism for this process. Explain whether ketone **B** would also racemize in basic solution.



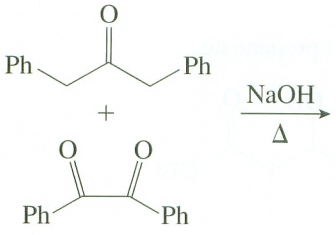
A



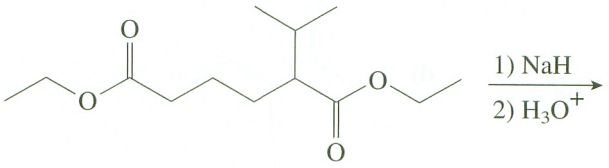
B

20.41 Show the products of these reactions:

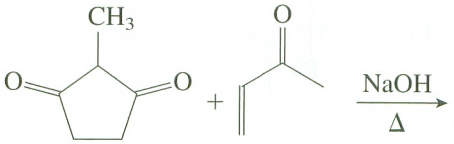
a)



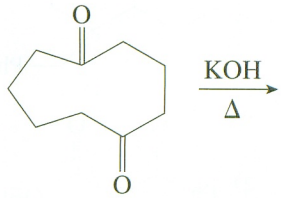
b)



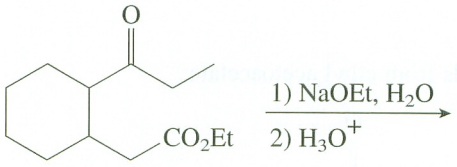
c)



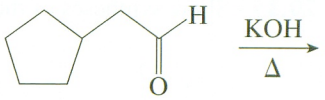
d)



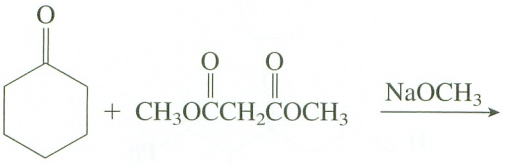
e)



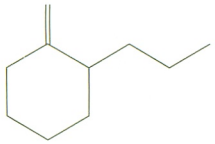
f) 2

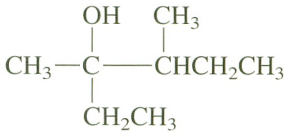


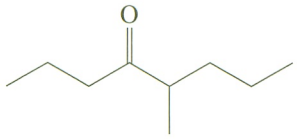
g)

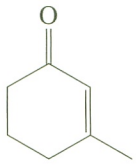


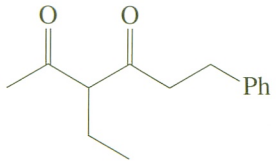
20.42 Show syntheses of these compounds from the indicated starting materials:

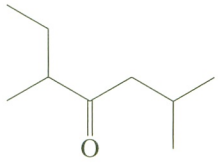
a)  from cyclohexanone

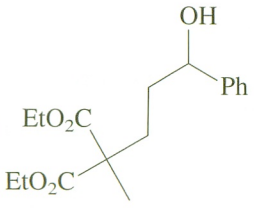
b)  from ethyl acetoacetate

c)  from butanoic acid

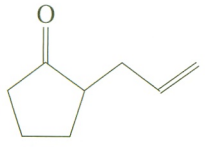
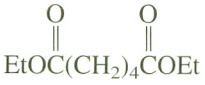
d)  from compounds without a ring

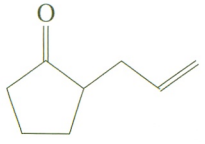
e)  from 2,4-pentanedione

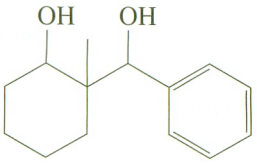
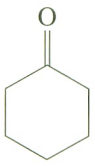
f)  from propanoic acid

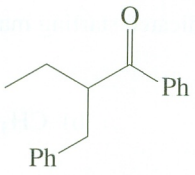
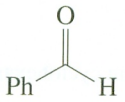
g)  from diethyl malonate

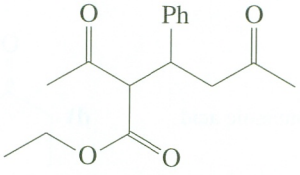
20.43 Show syntheses of these compounds from the indicated starting materials:

a)  from 

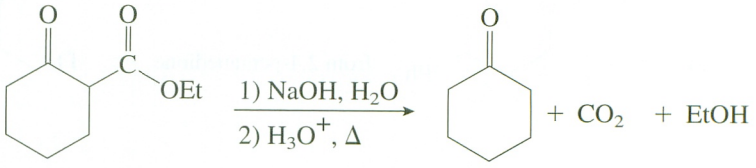
b)  from 

c)  from 

d)  from  and compounds with less than six carbons

e)  from 

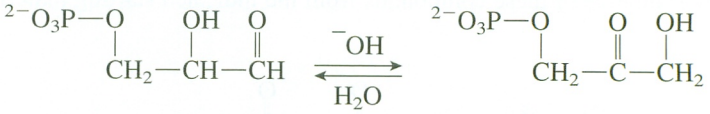
20.44 Show all of the steps in the mechanism for this reaction:



20.45 Show all of the steps in the mechanism for this reaction:

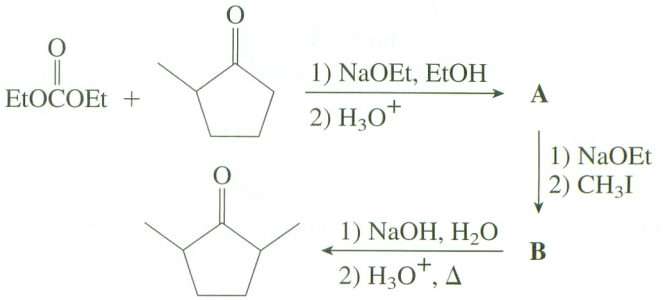
BioLink

20.46 Show a mechanism for the interconversion of glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) in basic solution:



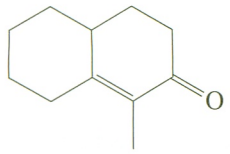
GAP DHAP

20.47 Show the missing products, **A** and **B,** in this reaction scheme and explain the regiochemistry of the reactions.

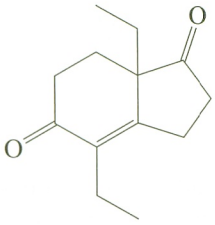


20.48 Show syntheses of these compounds using the Robinson annulation reaction:

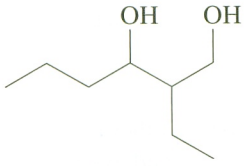
a)



b)

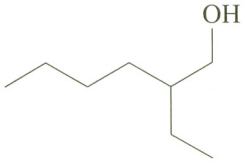


20.49 2-Ethyl-1,3-hexanediol is the active ingredient in the insect repellant "6-12." Suggest a synthesis of this compound from precursors with four or fewer carbons.



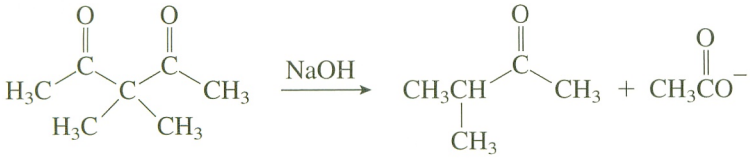
2-Ethyl-1,3-hexanediol

20.50 2-Ethyl-1-hexanol is used industrially as a plasticizer in the manufacture of plastics. Suggest a synthesis of this compound from precursors with four or fewer carbons.



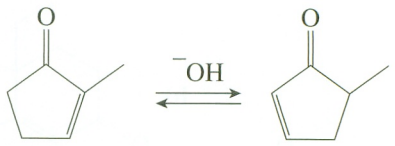
2-Ethyl-1-hexanol

20.51 Suggest a mechanism for this reaction:

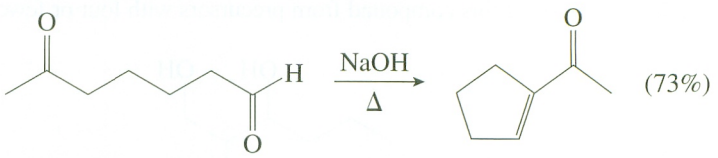


20.52 Deuterium can be incorporated at the positions α to a carbonyl group by reaction with D_2O in the presence of acid. Show a mechanism for this process. If the reaction were continued, what is the maximum number of deuterium atoms that would be incorporated into a single molecule?

20.53 Suggest a mechanism for this reaction:

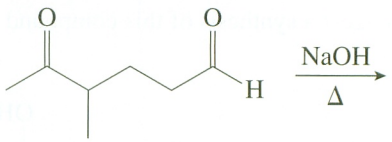


20.54 Intramolecular aldol condensations often present the possibility of the formation of several products. The reaction of 6-oxoheptanal gives the product shown in the following equation:

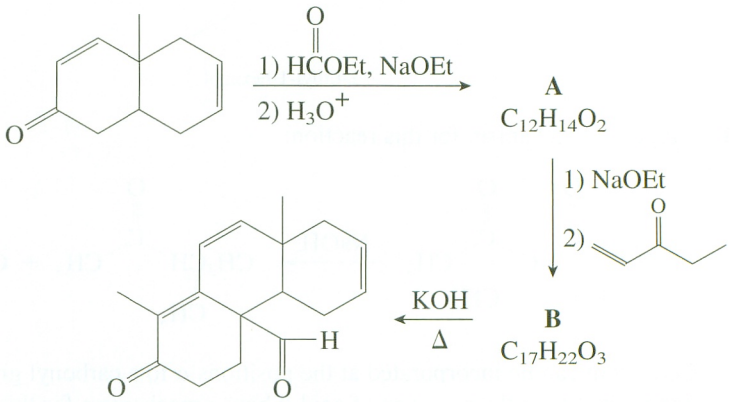


a) Show structures for the other α,β-unsaturated products that could be formed in this reaction and explain why the observed product is formed preferentially.

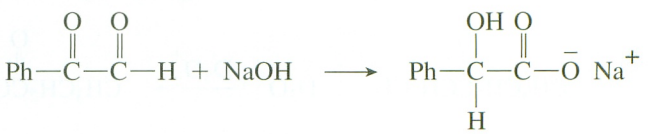
b) Predict the preferred product in this aldol cyclization:



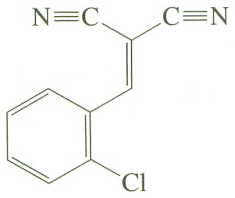
20.55 Show the missing products, **A** and **B,** in this reaction scheme:



20.56 Suggest a mechanism for this reaction:



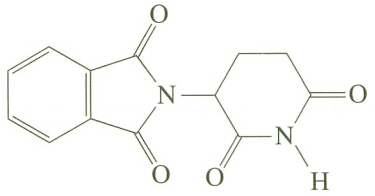
20.57 Suggest a synthesis of CS, a component of tear gas:



CS

20.58 Thalidomide was used to treat morning sickness in the late 1950s, but was soon discovered to have caused a number of birth defects. For a time it was believed that the birth defects were due to one enantiomer of this drug and that the other enantiomer was harmless. However, it was later found that either enantiomer will racemize under the acidic conditions of the stomach so the harmless enantiomer is converted to the harmful one. Suggest a mechanism for this racemization.

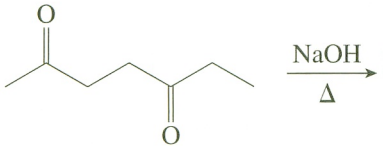
BioLink



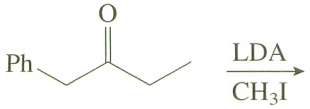
Thalidomide

Problems Involving Spectroscopy

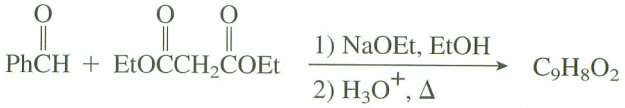
20.59 2,5-Heptanedione forms two products upon reaction with NaOH. Both products show a strong absorption near 1715 cm^{-1} in their IR spectra, and neither shows any absorption bands in the region of 3600 to 3300 cm^{-1}. The major product has singlets at 1.90 and 1.65 δ in its ^{1}H-NMR spectrum. Show structures for these products.

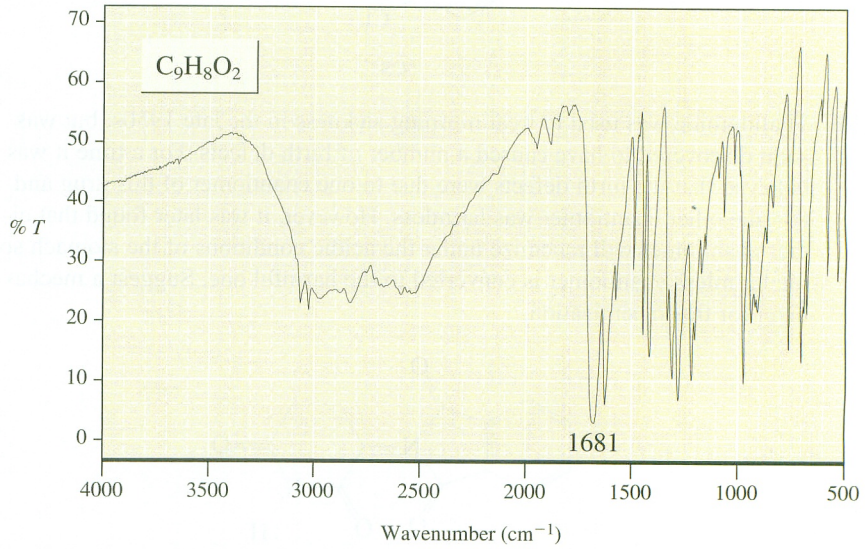


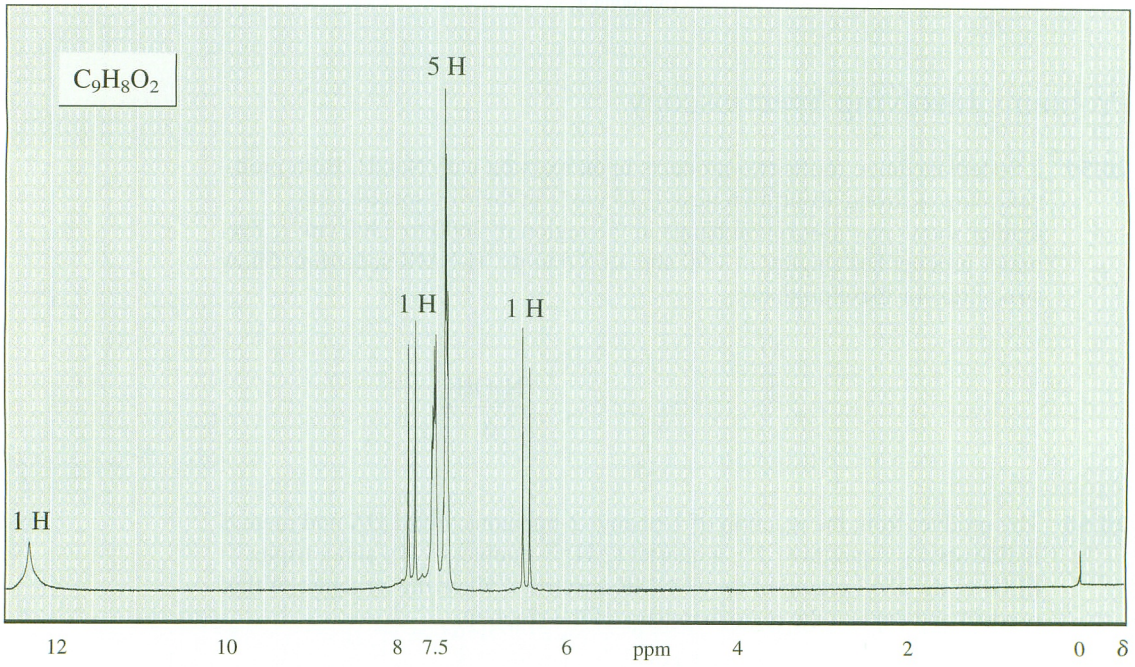
20.60 The product from the reaction of 1-phenyl-2-butanone with LDA and methyl iodide shows a quartet (1 H), a quartet (2 H), a doubtlet (3 H), and a triplet (3 H) in the alkyl region of its ^{1}H-NMR spectrum. Show the structure of this product and explain the regiochemistry of the reaction.



20.61 The IR and ^{1}H-NMR spectra of the product of this reaction follow. The formula of the product is $C_9H_8O_2$. Show the structure of the product.







Problems Using Online Three-Dimensional Molecular Models

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20.62 When either of these two stereoisomeric ketones is treated with NaOH, a mixture containing both of them is formed. Suggest a mechanism for this process. Explain which stereoisomer should be the major component of the mixture at equilibrium.

20.63 Reaction of 2-(3-bromopropyl)cyclopentanone with potassium *t*-butoxide gives the three products shown. Suggest a mechanism for the formation of each of the products.

20.64 The aldol condensation of 2-propanone (acetone) with two molecules of benzaldehyde forms the product shown. Explain the stereochemistry of the carbon–carbon double bonds in the product.